EARLY VERSUS DELAYED INITIATION OF ANTIRETROVIRAL THERAPY FOR HUMAN IMMUNO DEFICIENCY VIRUS AND TUBERCULOSIS COINFECTED INDIVIDUALS ON ANTI TUBERCULOSIS TREATMENT

Dissertation submitted to the Tamil Nadu Dr. M.G.R.

Medical University, Chennai – 600032

With partial fulfilment of the regulations for the award of Degree

M.D . GENERAL MEDICINE

BRANCH – I

DEPARTMENT OF MEDICINE

K.A.P.VISWANATHAM GOVERNMENT MEDICAL COLLEGE & M.G.M.GOVERNMENT HOSPITAL,

TIRUCHIRAPALLI.

APRIL 2015

BONAFIDE CERTIFICATE

Certified that the dissertation titled "**EARLY VERSUS DELAYED INITIATION OF ANTIRETROVIRAL THERAPY FOR HUMAN IMMUNO DEFICIENCY VIRUS AND TUBERCULOSIS COINFECTED INDIVIDUALS ON ANTITUBERCULOSIS TREATMENT"** is a bonafide work done by **Dr LAWRENCE. P,** under my guidance and supervision, in Partial fulfilment of regulations of The Tamil Nadu Dr. MGR Medical University for the award of M.D. Degree Branch I, (General Medicine) during the academic period from May 2012 to April 2015.

Prof .Dr.G.ANITHA. M.D
Unit chief M II
Department of General Medicine
K.A.P.V. Govt. Medical College
Tiruchirappalli.

Prof .P.KANAGARAJ.M.D
Professor & H.O.D
Department of General Medicine
K.A.P.V. Govt. Medical College
Tiruchirappalli.

The Dean

K.A.P.V. Govt. Medical College

Tiruchirappalli.

DECLARATION

I solemnly declare that the dissertation titled **"EARLY VERSUS DELAYED INITIATION OF ANTIRETROVIRAL THERAPY FOR HUMAN IMMUNO DEFICIENCY VIRUS AND TUBERCULOSIS COINFECTED INDIVIDUALS ON ANTITUBERCULOSIS TREATMENT"** was done by me at K.A.P.V Government Medical College, Tiruchirappalli under the guidance and supervision of **Prof. Dr.G.ANITHA.M.D.** The dissertation is submitted to the TamilNadu Dr. M.G.R. Medical University towards the partial fulfilment of the requirement for the award of M.D. Degree in General Medicine.

Place: Tiruchirappalli **Dr LAWRENCE.P**

Date :

ACKNOWLEDGEMENT

I sincerely thank **Prof. Dr. P. KARKUZHALI .M.D (PATH),** Dean K.A.P.V Govt. Medical College, Tiruchirappalli for having permitted me to undertake the study in this prestigious institution.

It is a great pleasure to express my sincere thanks to **Prof. Dr. P.KANAGARAJ, M.D.,** Head of the Department of Medicine for his guidance and encouragement.

With extreme gratitude, I express my indebtedness to my beloved unit Chief **Prof. Dr. G.ANITHA, M.D.,** for her motivation, advice and critical suggestions, which enabled me to complete this work.

I am thankful to other professors in Medicine **Prof. Dr.K.PARIMALADEVI, .M.D**., and **Prof. Dr.V.RAJENDRAN M.D.,** for their valuable guidance and motivation.

I am thankful to **Dr. N.K. SENTHILNATHAN**, **M.D.,** registrar, Department of Medicine for his valuable guidance and encouragement.

I gratefully acknowledge my indebtedness to **Dr. MANIVANNAN, MEDICAL OFFICER, ART CENTRE,** who helped me and gave me valuable guidance in doing this research.

I whole heartedly thank the assistant professors **Dr. M.RAJASEKAR, M.D.,** and **Dr .G.SATHISHKUMAR,M.D**., of my unit for their constant encouragement, constant guidance.

I thank my post graduate colleagues and CRRI'S for their help and suggestions.

I owe my sincere thanks to all the patients for their kind co-operation throughout the study

Last but not the least, I thank the Almighty for having made this possible.

CONTENTS

INTRODUCTION

Worldwide, Primary cause of death in HIV patients is Tuberculosis. Active tuberculosis seen in HIV positive patients than HIV negative patients by 100 times. Active tuberculosis is associated with high levels of plasma HIV RNA and reduced with anti tuberculosis treatment.HIV and TB co-infection itself can accelerate the course of other disease. The treatment of patients co-infected with HIV and TB requires careful management. Potential interactions between anti-tuberculosis and antiretroviral drugs may result in sub-therapeutic levels or toxicity. Relapse of tuberculosis and reactivation of TB is more common in HIV positive Individuals. This high burden of HIV/Tuberculosis co-infection is a concern as there is a higher risk of death for patients who are co-infected with HIV and Tuberculosis than those who either are only HIV-positive or only infected with TB .

It is necessary to understand the underlying epidemiology involved in transmission and disease progression to comprehend the synergy between the HIV and Tuberculosis and how one is fuelled by the other. The Provision of ART to TB patients with HIV is seen as a very important in addition to DOTS in preventing premature death and achieving the Millennium Development goals. Optimal time to initiate

EARLY VERSUS DELAYED INITIATION OF ANTIRETROVIRAL THERAPY FOR HUMAN IMMUNO DEFICIENCY VIRUS AND TUBERCULOSIS COINFECTED INDIVIDUALS ON ANTI TUBERCULOSIS TREATMENT

ABSTRACT

BACKGROUND:

For antiretroviral therapy (ART) naive human immunodeficiency virus (HIV) infected adults suffering from tuberculosis (TB), there is uncertainty about the optimal time to initiate highly active antiretroviral therapy (HAART) after startingantituberculosis treatment (ATT), in order to minimize mortality, HIV disease progression, and adverse events.The ART is started 2-8 weeks afterinitiation ATT IN patients with HIV-TB to minimise the chances of immune reconstitution inflammatory syndrome.

AIMS AND OBJECTIVES

- *To compare the incidence of IRIS, adverse effects, outcome of tuberculosis ,CD4 cell count, progression of HIV in early antiretroviral therapy and delayed antiretroviral therapy group with HIV TB co-infection on ATT.*
- *To decide optimal time to initiate ART in HIV TB co-infection on ATT*

MATERIALS AND METHODS

The study will be conducted among patients admitted to the in patient wards in the Department of Internal Medicine and those attending as out patients in a Tertiary Medical College Hospital who have been diagnosed as a case of HIV and Tuberculosis co infection.

TYPE OF STUDY:

Unicentric prospective study

EXPECTED RESULTS:

Early initiation of HAART for patients with HIV and TB significantly decreases incidence of HIV disease progression and has good tolerability.

USEFULNESS OF STUDY:

Worldwide approximately one third of all HIV related deaths are associated with TB,and TB is the primary cause of death for 10-15% of patients with HIVinfection.Patients with HIVINFECTION ARE MORE LIKELY TO HAVE ACTIVE TB ,BY A FACTOR OF 100 WHEN COMPARED WITH AN HIV NEGATIVE POPULATION .UNTREATED TB CAN ACCELERATE THE COURSE OF HIV INFECTION.

In this study early ART group

(within2 to 8 weeks after initiation of ATT) and late ART group (after 8 weeksof initiation of ATT) is compared for the incidence of IRIS, adverse effects, outcome of tuberculosis ,CD4 cell count ,progression of HIV.

This study will help us determine the optimal time to initiate ART in HIV-TB cases.

Keywords

HIV, Tuberculosis, Early ART, Delayed ART,

HIV- TB Co-infection

ART in HIV Tuberculosis co-infected individuals on ATT is still controversial. ART is usually started 2-8 weeks after initiation of ATT in patients with HIV-TB to minimise the chances of immune reconstitution inflammatory syndrome (IRIS).

In this study early ART group (within 2 to 8 weeks after initiation of ATT) and late ART group (after 8 weeks of initiation of ATT) is compared for the incidence of IRIS, adverse effects ,CD4 cell count ,progression of HIV, outcome of Tuberculosis. This study will help us determine the optimal time to initiate ART in HIV-TB cases.

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REVIEW OF LITERATURE

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HISTORY AND EPIDEMIOLOGY OF HIV

"33 years after the first reported cases of the acquired immunodeficiency syndrome(AIDS) and 30 years after the discovery of the etiologic agent, effective control of the HIV and AIDS pandemic remains elusive" .In June 1981, First CDC (centre of disease control) announced a new syndrome later coined "Acquired Immune Deficiency syndrome"[1, 2]. By 1983,the etiological agent for AIDS was identified and later named as human immunodeficiency virus (HIV) [3]. HIV disease pathogenesis is complex and multifactorial [4, 5].After HIV infection ,it enters into the lymphoid organs by viral replication [6, 7]. An immune mechanism usually inhibits viral replication within weeks, but the virus spurts from it, producing a chronic persistent infection leading to advanced clinical disease [8, 9].

A subspecies of chimpanzees native to Africa had been identified as the source of the virus. Scientists believe that simian immunodeficiency virus (called SIV) was transmitted to humans and mutated into HIV [10-12].There are 2 types of HIV:HIV-1 and HIV-2. Both types are transmitted by sexual contact, through blood, and from mother to child (more so for HIV-1 than HIV-2), and they appear to cause clinically indistinguishable AIDS. However, it seems that HIV-2have

incubation period less than HIV-1,chance of transmission is less than HIV-1

Worldwide, the predominant virus is HIV-1, and HIV-2 type is found mainly in West Africa and is rarely found elsewhere. The strains of HIV-1 can be classified into four groups:

1. "major" group M,

2. "outlier" group O

3. two new groups, N and P.

These groups are representing introductions of SIV to humans. M group is the most common cause of HIV in world. M group divided into 9 subtypes. These are8 subtypes A-K except E & I [13-15]. Two virus subtypes can meet and mix their genetic material to create a new hybrid virus in the cell of an infected person [16]. "circulating recombinant forms" is the virus that infect more than one person [17]. Several studies suggested that HIV-1 subtypes show distinct ecological distributions[18-23][24, 25]. Worldwide it has been shown that 48% of infections are caused by subtype C, 12% by subtype A, 11% by subtype B, 5% by subtype G, 2 % by subtype D and 22% recombinants [26].In 2010 ,34

million were with HIV and 2.7 million were new infections [27]. Worldwide decreasing new HIV infected individuals.

The reason for decreasing in trend are

1.HIV natural course

2. Antiretroviral therapy

3.behavioural change [28]

EPIDEMIOLOGY OF HIV IN INDIA [29]

2.4 million in India living with HIV next to South Africa. Men more affected than women0.3% of India's population living with HIV Prevalence in ANC is 0.6%Maharasthra,, Tamil Nadu, ,AP, ,Karnataka, Manipur and Nagaland having prevalence >1% in pregnant women

SUMMARY OF AIDS EPIDEMIC IN INDIA [29]

NUMBER OF PEOPLE LIVING WITH HIV	TOTAL	2.4 MILLION (1.9-3.0MILLION)
	MALE	61%
	FEMALE	35.5%
	CHILDREN	3.5%
PREVALENCE AMONG ADULTS	OVERALL	0.31%
	MALE	0.44%
	FEMALE	0.23%

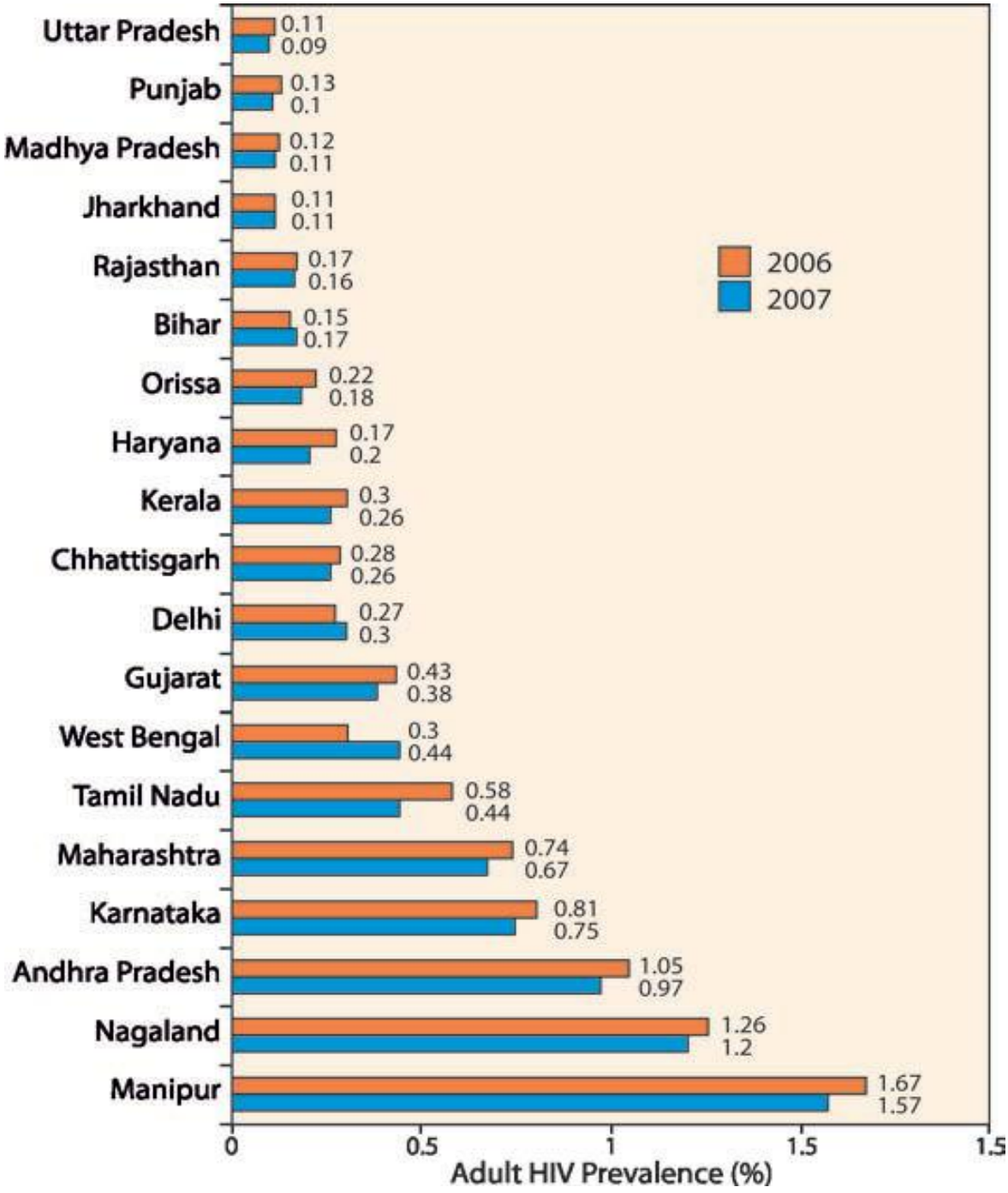


FIGURE 1:

STATE-WISE ESTIMATED ADULT HIV PREVALENCE, 2006-2007. [29]

PATHOGENESIS OF HIV INFECTION [30,31]

HIV enters and binds to DC which carry the virus to T helper or CD4 cells in lymphoid tissue establishing the infection. Human immunodeficiency virus targets and binds to the macrophages and CD 4 cells . After entry into CD4 cells it replicates within the cell. More helper cell are infected secondary to lysis and release new virus. During the course massive numbers of virus (>1billion/day) are released. The destruction of CD 4 cell count is the primary effect of HIV infection. CD4 cell destruction occurs in HIV infection, due to various mechanisms even in non HIV infected cell. Apoptosis and syncytium formed by membrane fusion of adjacent cells are the main mechanisms by which HIV destroys CD4 cells. This syncytium is short survived and seen in late stages of HIV infection. Virus and cytotoxic T cells destroy CD4 cell.

CD4 cell count decreases progressively during the course of HIV infection .Reverse transcriptase is used in conversion of viral RNA to DNA. By using integrase enzyme it is incorporated to human DNA. After replication using protease enzyme viral genomes are assembled.

HIV STRUCTURE

Human immune deficiency virus is an enveloped, positive stranded RNA virus, that measures 120 nm in diameter and consists of a lipid bilayer with uniformly arranged 72 spikes or knobs of glycoprotein – gp120 and gp 41 (HIV-1)/gp 36 (HIV-2). The virion gp120 located on the virus surface contains the binding site for cellular receptor(s). The two plus stranded RNA molecules are embedded in a protein capsid (p24) together with certain viral enzymes (viral RNA-dependent DNA polymerase (Pol, also called the reverse transcriptase, RT (p66, p51) and nucleocapsid proteins (p9, p7). The capsid (p24) is surrounded by a matrix layer (p17) that in turn is enclosed in lipid bi-layer, the envelope.

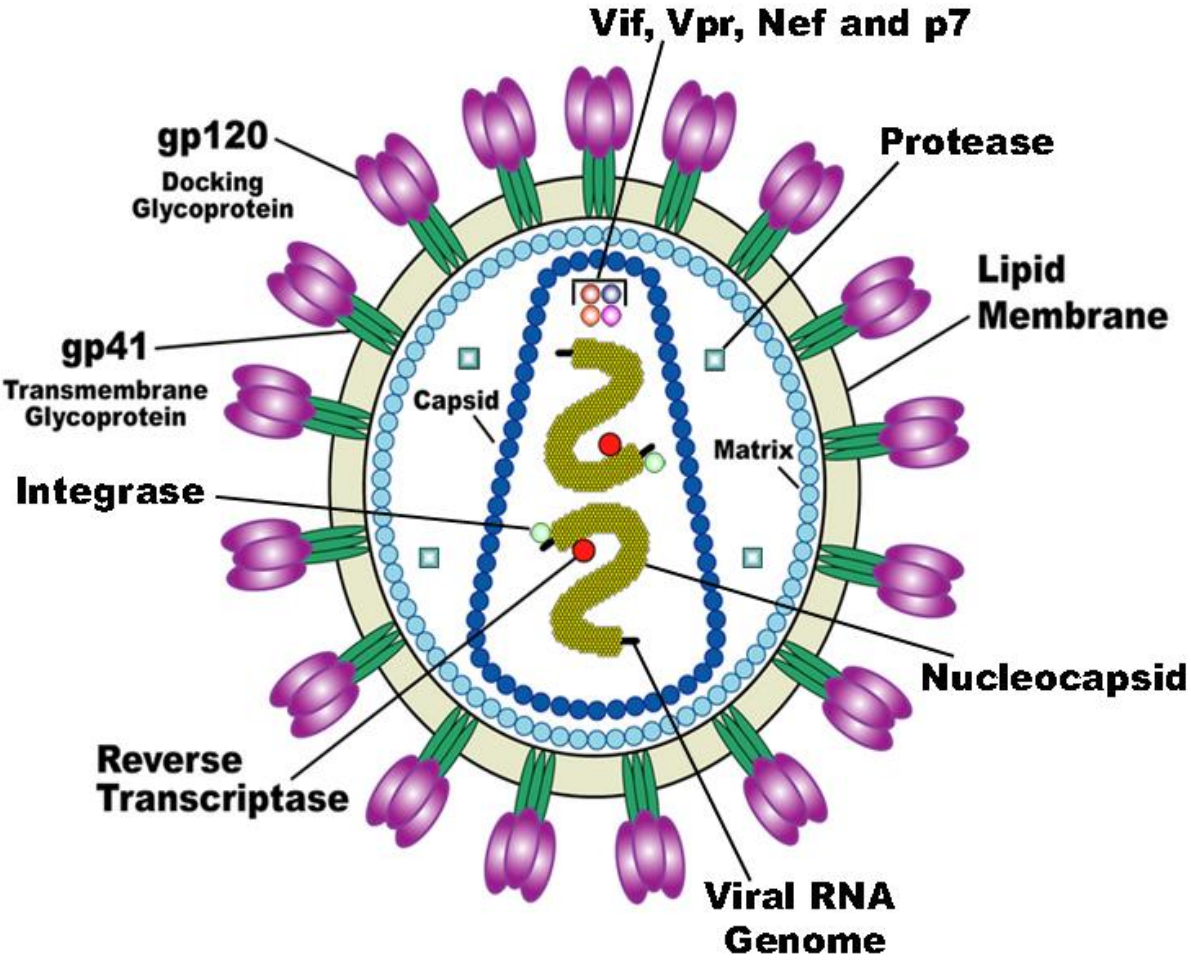


FIG 2: HIV VIRAL GENOME

1. The ***gag*** gene codes for the proteins p24, p17, p9 and p7.
2. The ***pol*** gene codes for the reverse transcriptase (RT),the protease (PR), and the integrase (IN) proteins.
3. The ***envelope*** gene codes for the gp120 and gp41 proteins which are made from a precursor gp160
4. ***Tat***, a transactivating protein, which along with certain cellular proteins, interacts with an RNA loop structure formed in the 3'portion of the virus and upregulates HIV replication.

The other regulatory protein which is needed for the synthesis of viral proteins:

1. ***Nef***(Negative factor), whose actual function remains unclear and is believed to down regulate viral expression.
2. The accessory HIV viral gene products and
3. ***vif, vpr, vpu/vpx*** appear to influence events such as assembly and budding, as well as infectivity involved in the production of infectious viruses.

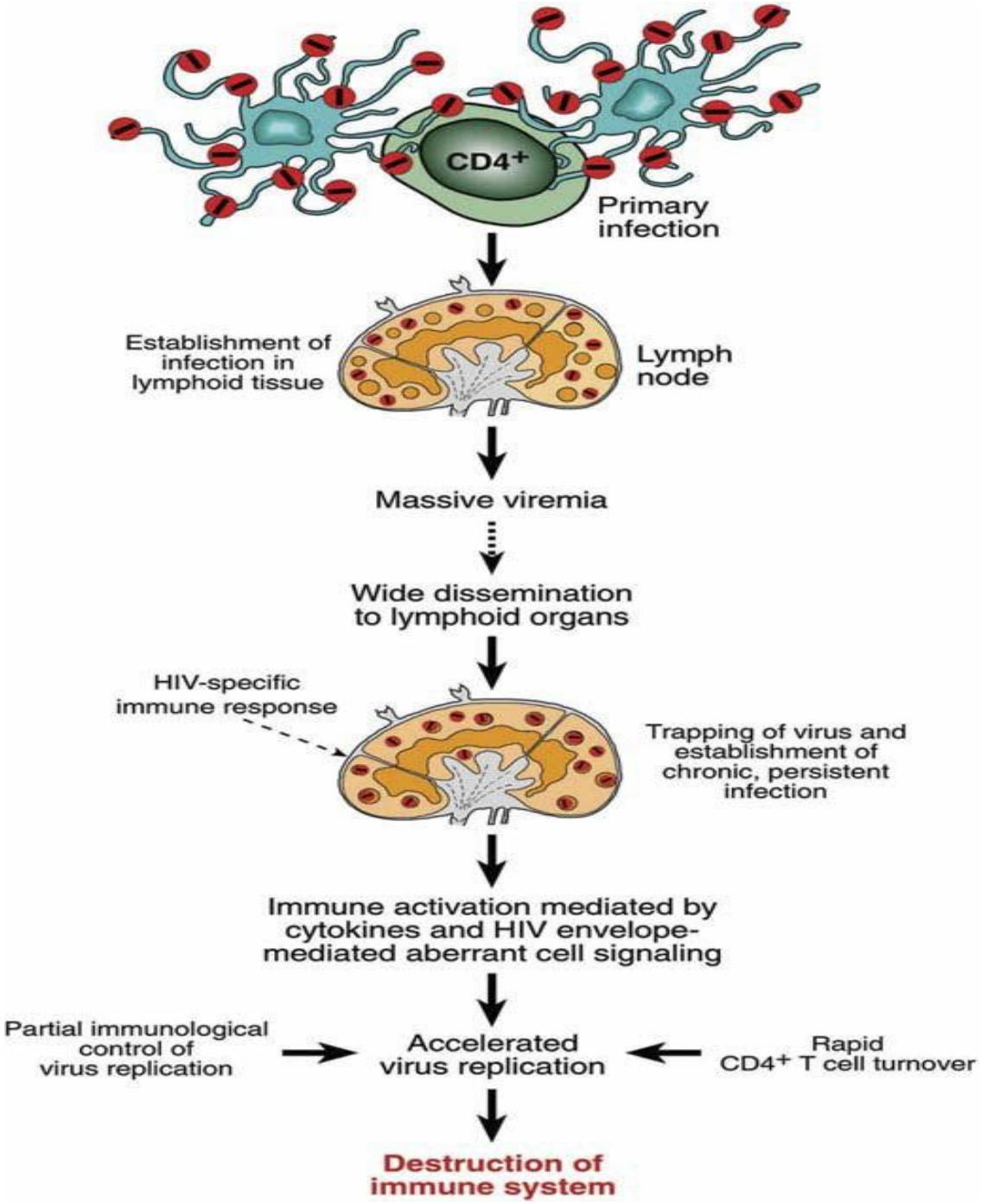


FIG 3: DETRUCTION OF THE IMMUNE SYSTEM [30]

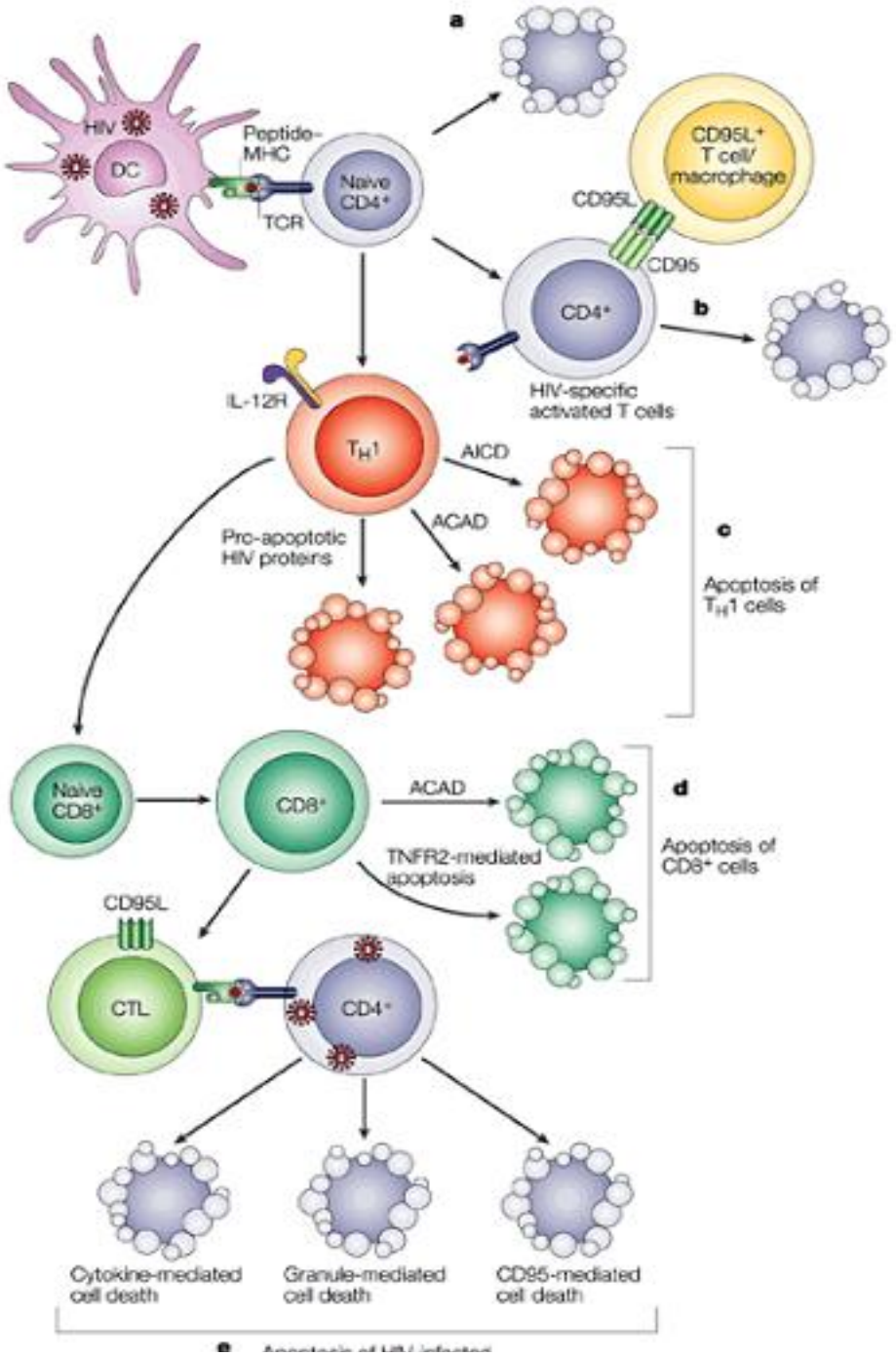


FIG 4: DESTRUCTION OF CD4 CELLS [31].

TRANSMISSION OF VIRUS

The primary routes of HIV transmission are through sexual intercourse, vertically from mother to infant during pregnancy or early infancy, per cutaneous exposure and exposure to infected blood and its products. In children, mother to child transmission (MTCT) is the major route[32]**]**

COMMON MODES OF TRANSMISSION OF HIV AND THEIR RELATIVE RISK[33]

Sl. No.	Types of Exposure	Approximate chance of infection per exposure
1	Sexual intercourse-anal, vaginal, oral	0.1 - 1.0%
2	Blood and blood products transfusion	> 90%
3	Tissue and organ donation: semen, cornea, bone marrow etc	50 - 90%
4	Injections and injuries: shared needles in IV drug users. Unsterile syringes and needles. Accidental injury to health personnel	0.5 - 1.0%
5	Mother to baby: Trans placental, at birth,	30%

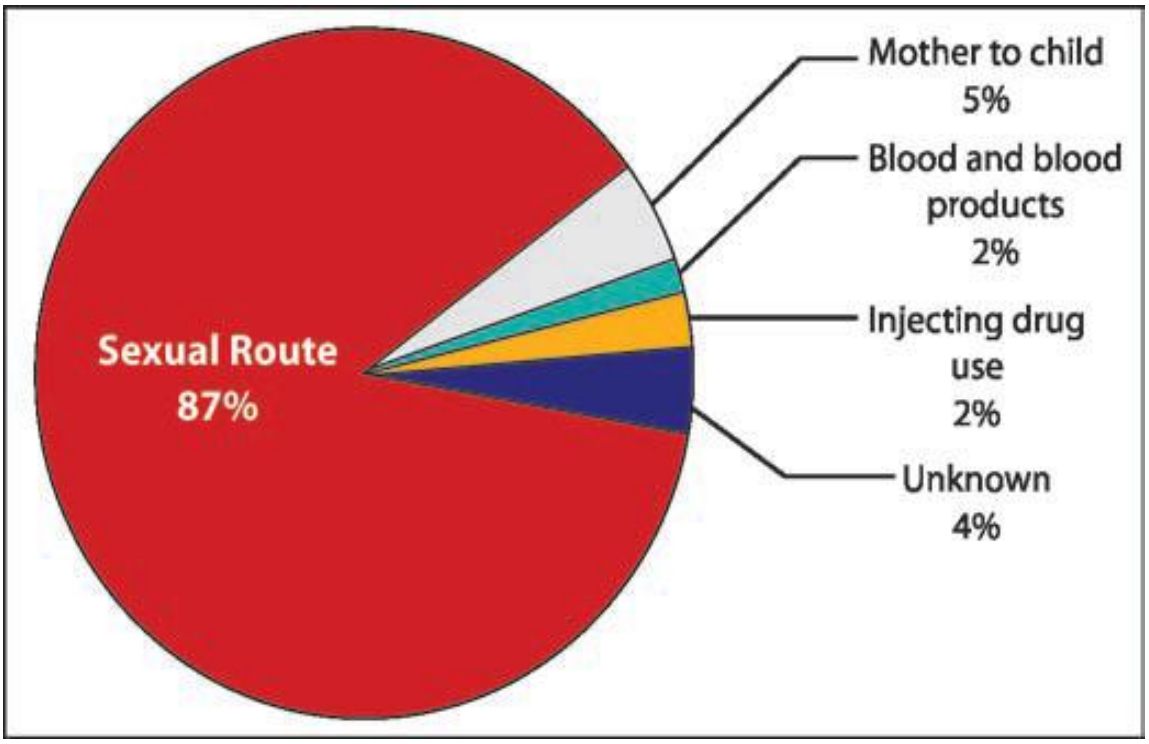


FIG 5: ROUTE OF TRANSMISSION [29]

PERIPHERAL BLOOD CD4 T LYMPHOCYTE COUNTS IN HEALTHY ADULT INDIANS [34]

CD4 T cells are the primary target cells for human immunodeficiency virus (HIV). Hence CD4T lymphocyte count is the important key marker of immune dysfunction in Human immunodeficiency virus disease progression. The measurement CD4 cell counts is useful to determine the initiation of HAART, to observe the efficacy of HAART and to initiate management for opportunistic infections . To develop the threshold levels of CD4 T cell counts, data from western countries are being used in India. Race and environment factors play a pivotal role in the CD4 T cell count. **So to understand immune dysfunction it is necessary to know ranges for the CD4cell counts in the study population**. **Flow cytometry** is the gold standard for the estimation ofCD4+ T cell counts due to its accuracy, precision and reproducibility and hence it is used widely.

The CD4 T cell count has been shown to be influenced by

1. Sex, age, race.

2.Time of specimen collection (diurnal rhythms)

3.Physical and psychological stress

4. Pregnancy

5.Drug administration (Zidovudine, Cephalosporin, Cancer chemotherapy, Nicotine and Steroids)

6. Tuberculosis

7. Viral infections,

8.Presenceof anti-lymphocyte auto antibodies and procedures like splenectomy.

Females tend to have higher CD4 cell counts than males; on contrary females have less CD8 cell counts than males. Although in adults, age does not have influence on CD4 cell counts significantly, lower CD4 cell counts may be observed in geriatric population. Even under strict quality control regime, the variations in CD4 T cell counts measured using different equipment and following different methodologies can be as high as 20 percent in controlled conditions with adequate technical expertise. Diurnal variation (the difference in the CD4 counts in the sample collected at different time points during 24 h period in the same individual) adds to this variation by as much as 20 per cent. **The lowest level of CD4 T cell counts was seen in the morning around 10.00 h and the highest at around 20.00 h. Hence for the sake of comparability of values it is recommended that the blood for CD4 T cell counts should always be drawn at the same time of the day in a given individual.**

CD4 T cells are also known to oscillate with vigorous physical activity. A study conducted in 20 healthy HIV-negative individuals showed significant reduction in the CD4 T lymphocyte count after rest for 1 hour. **As against absolute CD4 T cell count, CD4 per cent is found to be more stable with respect to time of the day, reagents, equipment used, gating strategies and biological factors that influence the CD4 counts.** Though CD4 per cent is not considered a good predictor of HIV disease progression, it indicates whether the rise or drop in CD4 Tcell count is a real change or just a fluctuation. The reported lowest value of CD4+ T cells count varied between 304 to 500 cells/µl and highest CD4 T cells count varied between 1000 cells/µl to as high as 1864 cells/µl indicating the wide difference that exists in the CD4 . The meanCD4 counts in the North India varied from as low as 703 to 818 cells/µl, in South India from 799 to 1048 cells/µl, in western India from 743 to 965 cells/µl and 848 cells/µl in Eastern India.

High risk behaviour of acquiring HIV when CD4:CD8 ratio is less than 0.85.However, the studies conducted in normal Indian populations showed variations in CD4:CD8 ratio from 0.04 to 3.5. The mean CD4: CD8 ratio varied between 0.94 to 1.78 in different studies. The ICMR multicentric study has reported a mean CD4:CD8 ratio of 1.2 from the six centres in different locations in India.

CD4 CELL COUNTS IN HUMAN IMMUNO DEFICIENCY VIRUS INFECTED INDIVIDUALS IN INDIA:

An Indian study showed that people infected with human immunodeficiency virus withCD4 T cell count of 200to 350 cells /µl had increased viral load than international AIDS Society suggestion and CD4T cell count cut off is 243 cells/µl reported in this study distinguished asymptomatic (CDC clinical category A) from symptomatic (CDC clinical category B) individuals.

In this study deferral of ART was associated with increased risk of death sixty nine percent of individuals with CD4 more than 350cells. In the light of this finding, the reference ranges might be of great importance in making decisions on the initiation of the ART.

CLINICAL FEATURES

The Human immunodeficiency virus infection pandemic consists of many separate epidemics. Physiologically, HIV infection more common in women than men by 4 times Mechanisms are

1. Semen which is infected remains in the cervix for longer time,
2. Large surface area in the vagina and cervix

3. The vagina is more susceptible to small tears during sexual contact
4. Young women's cervixes are even more vulnerable, particularly when they first start having sex.

Human immunodeficiency virus enters into infected cell, by using reverse transcriptase enzyme it forms DNA from RNA, incorporate into human DNA by integrase. It thus establishes a latent infection for the rest of the life of the infected individual. HIV is then activated to produce new virions whenever the infected CD4 cell is activated. An HIV coded protease is active in the maturation of the virions at the cell surface. This viral production disturbs CD4 cell function and eventually exhausts the CD4 cells leading to increased immunodeficiency and increased vulnerability to opportunistic infections and death. The symptoms are differing according to the stage of infection. Though PLWHA tend to be infectious in the first few months. The first few weeks after initial infection, individuals may have no symptoms flu-like illness including

1. fever
2. headache, rash
3. swollen lymph nodes, weight loss
4. diarrhoea
5. cough.
6. tuberculosis (TB)
7. cryptococcal meningitis

and in advanced stage cancers such as lymphomas and Kaposi's sarcoma. The most advanced stage of HIV infection is AIDS. It can take 10-15 years for an HIV-infected person to develop AIDS.

PROGRESS AND CLINICAL STAGES OF DISEASE [29]

Lymphocytes, MM series and DCs constitute the backbone of CMI. HIV affects almost all cells. The immune apparatus and function show the most obvious primary clinico-pathologic manifestations. Others which bear the primary brunt are the gastrointestinal tract (GIT) and CNS.

PATHOGENESIS OF IMMUNODEFICIENCY

THE VARYING PHASES OF IMMUNE REACTION

INCUBATION PERIOD

After transmucosal (and also parenteral) transmission, HIV reaches and establishes in T-cell areas of lymph nodes. Mucosal and nodal changes and early viral replication are clinically silent. Viral release into circulation increases slowly. Viral antigens appear in blood. HIV infection clinically manifests in 3 to 6 weeks post-exposure in up to 90% cases.

ACUTE RETROVIRAL SYNDROME (ARVS)

Increasing viraemia makes the infection manifest as ‘flu like’ episode, called ARVS (sore throat, myalgia, fever, rash, fatigue, enlarged nodes, diarrhoea and vomiting). Proportionate to the viral load in blood, there is a downward spike in CD4 count. With virus dissemination to all lymph depots, the infection becomes multi-systemic and permanent. Due to the host’s immune response, viral replication is restrained. Symptoms abate in 2 to 4 weeks. CD4 count gets corrected. Patient is sero-converted. He may be diagnosable, also by virus its components in blood. After recovery, the patient goes through a variable period of clinical latency. Two types of ‘latent’ phases are possible.

VIRUS NON-PRODUCTIVE LATENT (VNPL) PHASE

Persons with a strong immune response take care of total viral replication while the virus lurks in reservoirs, in peaceful coexistence, awaiting an opportunity to reactivate. This can continue for months to years. The patient is sero-positive, has no viral load in blood and has a normal immune profile. Cases in VNPL phase are clinically healthy and symptom-free. They may even be non-infective to sex partners but are not safe blood donors.

VIRUS LOW-PRODUCTIVE SUBDUED (VLPS) PHASE

If the initial immune response is not strong enough to restrain viral replication completely, virus is produced in minute amount, but not sufficient to produce continuous clinical manifestations. The virus keeps on infecting new CD4 T-cells. Its replication steadily increases without causing a drop in their count. A period of apparent inaction continues over a variable period, depending upon the magnitude of viral replication. Patient is sero-positive. His viral load depends on the 'set point'. CD4 count, usually normal, shows a trend of gradual annual decline (25 to60 cells per year).Cases in VLPS phase are not totally symptom-free. They may have mild/moderate episodes of symptoms due to GIT lesions. In between the episodes, they do not appear seriously ill. There may be 'non-alarming' weight loss. Their infectivity is proportional to viral load.

PERSISTENT GENERALISED LYMPH ADENOPATHY (PGLA)

Some cases in VLPS phase have PGLA. Enlarged nodes show nonspecific polyclonal hyperplasia of 'B' and 'T' cell areas. Abnormal antibodies and their effects may appear. Some cases may have few, mild symptoms (fever, rash, fatigue). Constitutional symptoms indicate that the next stage is imminent very soon.

STAGE OF IMMUNODEFICIENCY (SIMD)

Viral replication continues over a long period, playing havoc with the immune apparatus. **CD4 T-cells play the role of an 'orchestra conductor' for humoral immunity as well as CMI**. Dysfunction of humoral immunity is *indirect* due to influences on B-cells. Dysfunction of CMI is the direct result of loss of T lymphocytes. Progressive, relentless loss and dysfunction of almost all subsets of immune competent T-cells are the major events. Lymph nodes, thymus, bone marrow, lymphoid depots in tissues and gastrointestinal tract get depleted of T-cells. They show structural disorganisation and atrophy. CD4 and CD8 cell counts in blood drop. **SIMD invites opportunistic pathogens and activates the pre-existing latent ones. CD4 count in peripheral blood is used as an indicator of immune function**.

It is however not a perfect guide. 2% of the total pool of CD4 cells is in blood; rest are in tissues. Even a minute change in the distribution can bring about a vast change in the count. In some studies, CD4 percentage was a better marker than CD4 count. As of today, CD4 count is used and has served as a useful practical guide. The Time required for progress from infection to SIMD is variable. It depends on the summation of dynamics of viral replication and the host's anti-HIV immune response. It can be prolonged by ART regime. Usually, the period cannot

be predicted with certainty, except in cases in VLPS, showing decline of CD4 count at a steady rate. SIMD is reached in 2 to 5 years in 'rapid progressors'. 'Slow progressors' take more than 10 years. 8 to10 years is the period required for majority of the cases. Hallmarks of SIMD are increasing viral load, increasing titer of viral components in blood and CD4 count below 300/mL. Anill-understood group consists of patients in whom CD4 counts are below 300/mL and yet who show no manifestations of immunodeficiency. **Co-existing STD/TB/viral infections accelerate the onset of SIMD. SIMD aggravates these diseases. A vicious cycle is thus established.**

POSSIBLE CO-MORBIDITIES ASSOCIATED WITH HIV

These are immune complex lesions, autoimmune lesions and hypergammaglobulinaemia.

CLINICAL STAGING:

This staging system has been developed since many countries and communities are not having facilities for CD 4 count

Stage I:

1. Persistent generalized lymphadenopathy

2.Asymptomatic

Stage II:

1.Herpes zoster

2. Angular chelitis

3.Recurrent oral ulceration

4. Papular pruritic eruptions

5.weight loss under 10% of body weight

6.Recurrent respiratory tract infections

7.Fungal nail infections

8.Seborrhoeic dermatitis

Stage III:

1.PTB

2 Severe pneumonia, empyema, pyomyositis, bone infection, meningitis, bacteraemia

3.Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

4.Weight loss over 10% of presumed or measured body weight

5.Chronic diarrhoea for longer than one month

6.Fever- intermittent or constant for longer than one month

7.Oral candidiasis

8.Oral hairy leukoplakia

9.Severe unexplained anaemia (below 8 g/dl), neutropenia (below 0.5 billion/l)chronic thrombocytopenia (below 50 billion/l)

Stage IV:

1.Extrapulmonary cryptococcosis including meningitis

2.Disseminated non-tuberculous mycobacteria infection

3.Progressive multifocal leukoencephalopathy

4.Chronic cryptosporidiosis

5.Extrapulmonary tuberculosis

6.Kaposi sarcoma

7.Cytomegalovirus infection (retinitis or infection of other organs)

8.HIV wasting syndrome

9.Pneumocystis pneumonia

10.Recurrent severe bacterial pneumonia

11.Central nervous system toxoplasmosis

12.HIV encephalopathy

13.Chronic herpes simplex infection

14.Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs

15.Lymphoma (cerebral or B cell non-Hodgkin)

16.Invasive cervical carcinoma

17.Atypical disseminated leishmaniasis

18.HIVnephropathy

19.Chronicisosporiasis

20.Extrapulmonaryhistoplasmosis, coccidiomycosis

21.Recurrent septicaemia

DIAGNOSIS OF HIV

The World Health Organization (WHO) recommends the use of immunological assays for the diagnosis of HIV [35,36]. Immunological assays include ELISA and WESTERNBLOT ASSAY. ELISA used as screening test it should not be used as confirmatory test. WESTERN BLOT is confirmative diagnostic test . In children less than 18 months of age virological assays can be used for screening to determine HIV infection against the background of antibodies transmitted from the mother [37].

TREATMENT OF HIV

The most advances in Human immunodeficiency treatment have come from inhibiting enzyme activity .used by the HIV in its life cycle. ART drugs are broadly classified by the site of drug action.

Entry or fusion inhibitors interfere with fusion and replication of HIV into the infected cell. The CCR5 receptor antagonists bind to theCCR5 receptor on the surface of the CD4T-cell thereby blocking viral attachment to the Cell do not target the virus directly .

Nucleoside reverse transcriptase inhibitors (NRTI) inhibit reverse transcriptase by incorporating into viral DNA strand .NRTI are competitive inhibitors. The non- nucleoside reverse transcriptase inhibitors (NNRTI) are non-competitive inhibitors of reverse transcriptase enzyme. The protease inhibitors (PI) act by inhibiting the protease enzyme which is essential for assembly of new virions.

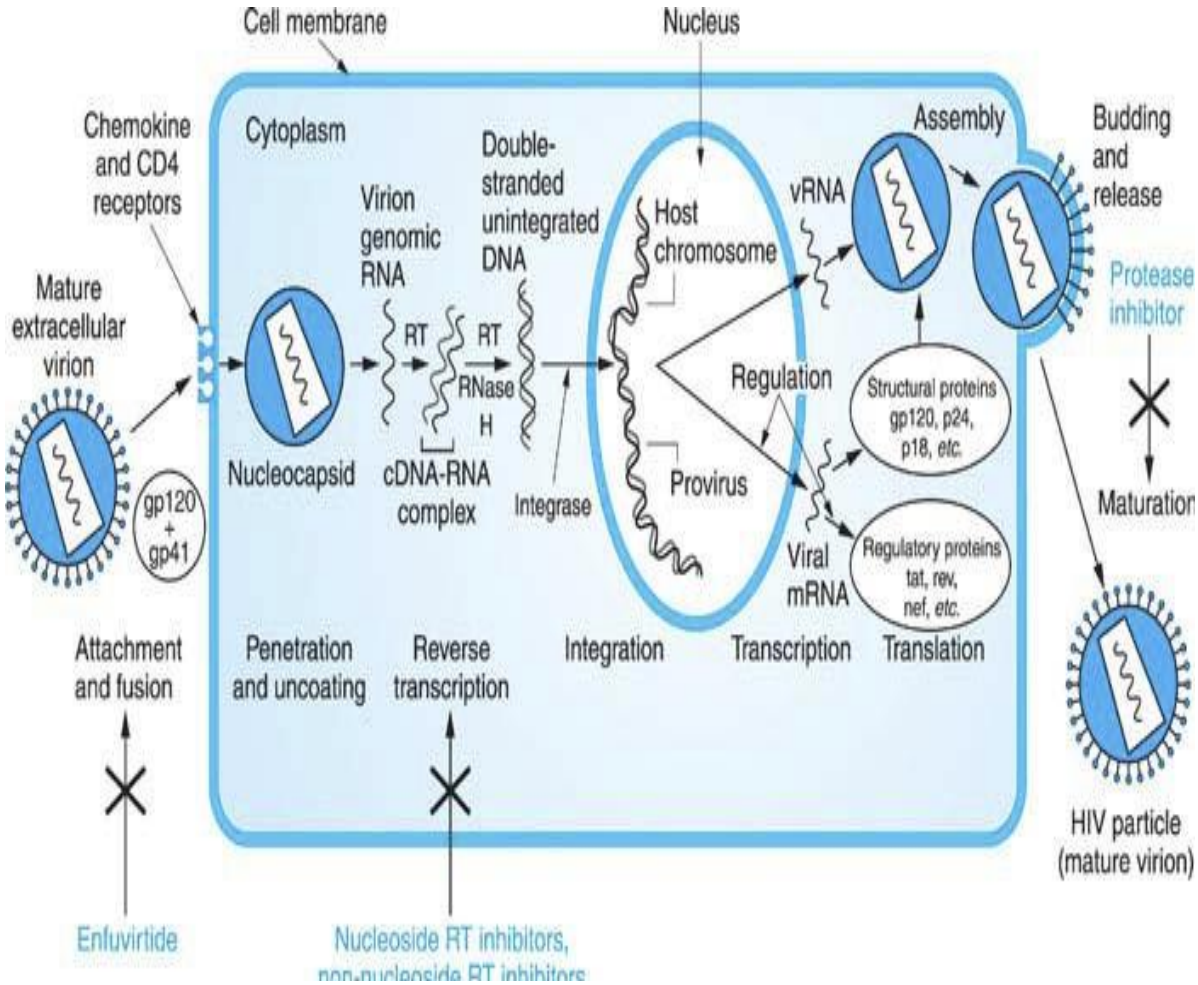


FIG 6: Diagram showing HIV Life Cycle & Sites of Action Antiretroviral drug

Integrase enzyme useful in integration of viral DNA into DNA of infected host cell. So RALTEGAVIR which is integrase inhibitors will be useful in the treatment of HIV . The maturation inhibitors(BEVIRIMAT) bind with gag protein result in blocking the conversion of the polyprotein into the mature capsid protein (p24).In 1987, Zidovudine is the first drug approved for Food and Drug Administration(FDA) which inhibits the reverse transcriptase . This was used as a monotherapy for several years with very limited efficacy and later it was successfully paired with lamivudine (3TC) and used as combination therapy. The discovery of other classes of antiretroviral drugs and potential development of resistance and cross-resistance to monotherapy warranted a switch from monotherapy to combination therapy. The introduction of viral load determination was crucial to prove this concept. This switch to combination antiretroviral therapy – highly active antiretroviral therapy (HAART)combination therapy prevents mutated forms of Human immunodeficiency virus from evolving.

Currently there are six classes of antiretrovirals with over 26 different drugs used for treatment of HIV. These drugs are aimed at stopping HIV in its tracks by stopping the various stages of viral

replication. These classes include nucleoside reverse transcriptase inhibitors (NRTI's) – Zidovudine

1. Non-nucleoside reverse transcriptase inhibitors(NNRTI's)-Efavirenz
2. Protease inhibitors (PI's)-Loprinavir
3. Fusion inhibitors-Enfuviritide
4. CCR5 antagonists –Aplaviroc
5. Integrase inhibitors-Raltegavir [33-35]

By the end of 2010, WHO reported that in middle and low income countries ART issued for 6,650,000 people accounting for 47% coverage [38].Guidelines have been set forth by the WHO and each individual country on how to use and manage patients on HAART [39]. WHO recommended first-line therapy consist of an non nucleoside reverse transcriptase inhibitor plus two Nucleoside reverse transcriptase inhibitor, one of which should be Zidovudine or Tenofovir . Stavudine less commonly used in first-line regimens because of its well-recognized toxicities. Second-line ART consists of a ritonavir-boosted protease inhibitor (PI) plus two NRTIs, atazanavir or lopinavirare the preferred PIs [39].

NACO GUIDELINES ON INITIATION OF ART

WHO Stage	WHEN CD4 COUNT NOT AVAILABLE	CD4 count (cells/mm^3)
I.	Do not treat	Treat if CD4T cell count< 250 (If between251-300, repeat it after 4 weeks)
II.	Do not treat	
III.	Treat	Treat if CD4T cell count < 350
IV.	Treat	Treat irrespective of CD4T cell count

1. HIV/AIDS &TB (Regimen should contain efavirenz):

Pulmonary Tuberculosis & HIV/AIDS- start Anti retroviral therapy after 2 wks of initiation of Anti tuberculosis treatment for all patients with CD4 < 350 cells/mm3.(for patients with CD4more than 350, defer ART.).Extra Pulmonary TB & HIV- start Anti retroviral therapy after 2 wks of initiation of Anti Tuberculosis treatment in all patients irrespective of CD4 count Currently the guide line mentions that if CD4 >350, the patient needs to be re assessed for CD4 and clinical stage at completion of ATT.

PREVENTIVE MEASURES FOR HIV

The rate of new HIV infections and AIDS-related deaths has fallen globally resulting in a decline of the epidemic. Declines in new Human immunodeficiency virus infections across the world have been reduced by access to antiretroviral therapy and the changes in behaviour via several intervention programs. ART coverage dramatically increased in sub-saharan Africa 20% alone from 2009 to 2010. The best success seen is in programs to prevent the MTCT which can decrease rates of transmission by 92-99%[40,41]. Preventing measures of MTCT

1. USE of a combination of antiretrovirals during pregnancy
2. After birth in the infant potentially include bottle-feeding rather than Breastfeeding.

No vaccine identified till now. However further research is on-going in search of a truly effective vaccine [42,43]. Social strategies have proved effective in changing people's behaviour including sex education, provision of condoms both male and female, needle exchange programs, HIV testing centres, treatment of sexually transmitted infections and the use of social media to educate people. These strategies have widely differing levels of efficacy and social acceptance.

Other interventions include advocating male circumcision and the potential use of an antiretroviral based vaginal gel. Circumcision in men has been shown to reduce the risk of HIV infection in heterosexual men by between 38-66%.World health organisation and United nation AIDS recommend to prevent female to male HIV Transmission by circumcision [44]. Provision of HAART as pre-exposure prophylaxis has been shown to protect 96% of partners of HIV infected individuals . Post exposure prophylaxis with HAART is also recommended following needle-stick injuries or exposure to body fluids within the health care environment and to sexual assault victims. A Tenofovir containing vaginal gel, when used immediately before sex, reduces infection rates by approximately 40% [45].

TUBERCULOSIS

HISTORY AND EPIDEMIOLOGY OF TUBERCULOSIS

"With 2 billion persons, a third of the world population are estimated to be infected with mycobacteria" [46].The presence of tuberculosis (TB) can be traced back to centuries ago. Recently near eastern Mediterranean Scientists discovered the evidence of TB infection which is present since 9000 years ago[47]. Over time, tuberculosis was known by many names including

1. Contagion,
2. Phthisis and
3. White Plague.

Scientists at the time believed death by tuberculosis was inevitable and that it was a contagious disease characterized by fever, cough with expectoration , and decreased appetite and loss of weight [48]. It was not until 1882 when a physician Robert Koch identified the casual agent of disease *Mycobacterium tuberculosis*, or Koch's bacillus by using a new staining method [49,50]. So March 24 known as World Tuberculosis Day [51].

Streptomycin is the first effective anti-tuberculosis agent, was isolated from organism and used for treatment of TB [52]. Although this monotherapy cured several people, a substantial number of people developed TB again (relapse) and later resistance to streptomycin was seen [53]. Streptomycin in combination with isonicotinic acid hydrazide (isoniazid) showed much better outcomes and after rifampicin was discovered in 1957 the TB treatment was revolutionized [54-56]. Ultimately, results of clinical trials led by the BMRC showed that a 4

drug regimen including rifampicin and isoniazid the most effective and reasonably well-tolerated oral agents for active tuberculosis [57].

One in three people in the world is infected with *Mycobacterium tuberculosis,* however a relatively small proportion of infected people will go on to develop TB disease[58].

Tuberculosis remains a public health problem .Despite the availability of highly efficacious treatment for decades, . In 1993, World Health Organisation declared Tuberculosis a global public health emergency, at a time when an estimated seven to eight million cases and one and half million deaths occurred each year. There are 22 countries in the world which constitute 82% of global tuberculosis cases, and these are termed as 22 High-TB Burden countries. There were an estimated 88lakhs incident cases of Tuberculosis globally in 2010 [59].Tuberculosis is the second leading cause of death from an infectious disease worldwide (after HIV), which caused an estimated 1.5 million deaths in 2010. Globally, decreasing in absolute number of occurrence of tuberculosis at an approximate rate of 1.3%per year since 2002. Likewise TB mortality has also been falling globally [60]. In 2010, 6.2 million people notified to NTCP as tuberculosis infected people. Of these, new one is 5.4 million, recurrent episode is 0.3 million. Globally, the ratio of Male to female ratio TB cases notified is 1.7.

TRANSMISSION OF TB, THE SYMPTOMS AND SIGNS

Mycobacterium tuberculosis (rod-shaped, non–spore-forming, aerobic bacterium) is spread by small airborne droplets, called droplet nuclei, generated by the coughing, sneezing, talking, or singing of a person with pulmonary or laryngeal tuberculosis. Factors influencing transmission:

1. Number of bacilli in the droplets
2. Virulence of the bacilli, exposure of the bacilli to contact
3. Ultraviolet light
4. Degree of ventilation.

Introduction of *Mycobacterium tuberculosis* leads to pneumonia, it can spread to pleura , lymphatics, central nervous system, bone, joints. For persons with immune competent individuals(intact CMI) the next defensive step is granuloma formation around the *Mycobacterium tuberculosis* organisms restricting growth and establishing latency, leads to healed lesions by the process of fibrosis and calcification. Primary progressive tuberculosis is developed in Immune compromised patients [86, 87].Even though many people infected with tuberculosis bacilli only 10% will develop disease[88].

General signs and symptoms

1. Fever, chills, night sweats
2. Loss of appetite,
3. Weight loss
4. Fatigue
5. Finger clubbing may also occur .

In patients with pulmonary TB along with the general symptoms they may also present with chest pain and coughing out blood. EPTB occurs more commonly in immunosuppressed persons, commonly HIV patients and in young children. Common sites for extrapulmonary infection include the pleura, central nervous system(CNS) , lymphatic system, genitourinary system (GIT), and the bones and joints among others. More severe form of TB is called "Disseminated or Miliary TB" makes up about 10% of extrapulmonary cases. Other signs of EPTB depend on the affected organs.

DIAGNOSIS OF TB

Active TB may be considered as a possible diagnosis when patients present with physical signs and symptoms suggestive of TB plus abnormal findings on a chest radiograph. The chest x-ray may show upper and middle lobe infiltrates and cavitations; however atypical

features may be seen in immuno-compromised patients. Traditionally, in spite of modern advances, microscopic examination of a sputum smear or other diagnostic specimen for the Existence of AFB using the Ziehl-Neelson staining is used to identify active TB. Identification of mycobacterium tuberculosis in culture medium is the confirmatory test. Löwenstein-Jensen , or Kirchner and the various Middlebrook formulations &New MB/BacT (Biomerieux),BACTEC 9000 (BectonDickinson), and the Mycobacterial Growth Indicator Tube are used for culture the organism. [61].

Newer rapid automated DNA tests are being used for the diagnosis of TB along with drug susceptibility testing . Presumptive diagnosis of pulmonary TB can be made in patients with abnormal findings on a chest radiograph suggestive of TB, presenting with signs and symptoms of TB in spite of at least two acid fast bacilli smear negative.

Diagnostic criteria for Pulmonary TB should include:

1. Radiographic abnormalities consistent with active pulmonary TB
2. No response to a course of broad-spectrum antibiotics
3. A decision by a clinician to treat with a full course of anti-TB chemotherapy.

4. A patient with positive culture but negative AFB sputum examinations is also a smear-negative case of pulmonary TB

Extra pulmonary tuberculosis diagnosis based on

1. one culture-positive specimen
2. Histological or strong clinical evidence consistent with active Extrapulmonary disease
3. decision by a clinician to treat with a full course of anti-tuberculosis treatment.

Immunological diagnostic tests such as the Mantoux tuberculin skin test are of limited application due to cross reactivity and poor sensitivity.

TREATMENT OF TB

Directly Observed Treatment, Short-course (DOTS) was adopted by WHO and implemented in several countries and has been the gold standard of treatment [62]. According to DOTS Observer should observe at least initial 2 months of ATT &watching patients swallow their TB therapy. If DOTS has been implemented properly success rate may exceeding 95%.

WHO has set up guidelines whose primary aim is to help NTCP in setting Anti tuberculous treatment strategies. The first line drugs in the treatment of TB are rifampicin, isoniazid, ethambutol and pyrazinamide. The second line consists of 6 classes of drugs including aminoglycosides, polypeptides, fluoroquinolones and thioamides. TB treatment is divided into a 2 months intensive phase that comprises all the 4 first line anti-TB drugs followed by 4 months continuation phase with rifampicin and isoniazid (2HRZE/4HR). WHO now recommends less chances of relapse and failure with 24 weeks course of Rifampicin However, despite all measures, the tuberculosis that is resistant against atleast to firstline anti-tuberculosis treatment that is defined as multiple drug resistant tuberculosis (MDRTB)(is resistant at least to isoniazid and Rifampicin, the two most powerful first-line anti-TB drugs has been on the increase) . MDR-TB can develop in sensitive Tuberculosis and this is always due to Poor compliance of ATT . 20 months of ATT including second line drugs are recommended for MDR-TB . In 2006, WHO announced a new epidemic of Extensively Drug Resistant Tuberculosis XDR-TB is defined as resistance against RIFAMPICIN , ISONIAZID ,any member of the QUINOLONE family and at least one of the following second-line anti-tuberculosis injectable drugs: KANAMYCIN, CAPREOMYCIN, OR AMIKACIN .

HIV prevalence is closely associated with this type of tuberculosis. Currently the only available and most widely used vaccine is the BCG which, while it is effective against disseminated Tuberculosis in childhood [63].

HIV AND TB CO-INFECTION

EPIDEMIOLOGY OF HIV AND TB CO-INFECTION

The HIV epidemic worsens the already presentTuberculosis problem in poor countries it also reviving old Tuberculosis in well resourced countries .**Both TB and HIV are fatally synergistic**. TB is the leading infectious killer of PLWHA and the most common opportunistic infection (OI) [64,65]. Almost one in four deaths that occurs among PLWHA is due to Tuberculosis. Human immunodeficiency virus promotes both the progression of latent Tuberculosis infection to active disease and a relapse of the disease in previously treated patients: HIV positive patients developed disease from tuberculosis infection 20-30 times than HIV negative [66-69]. HIV affects the immune system and increases the probability of people acquiring new Tuberculosis infections. Tuberculosis may accelerate the progression of Human immune deficiency virus from asymptomatic to symptomatic disease and

even AIDS, increases both mortality and the incidence of other opportunistic infections among PLWHA.

Globally the number of TB patients who had been diagnosed with Human immunodeficiency virus status reached2.1 million in 2010, equivalent to 34% of notified cases of Tuberculosis. Of the 8.8 million incident cases globally an estimated 1.1 million (13%) were found to be co-infected with HIV People with smear negative PTB &EPTB have high mortality rate since they are immune suppressed than smear positive PTB . Mortality rate reduced with anti retroviral therapy .Life expectancy and quality of life improved with ART.

THE IMPACT OF HIV CO-INFECTION AND ART IN TB PATIENTS

In the presence of HIV-TB co-infection is associated with high mortality and morbidity, despite effective tuberculosis therapy. However, studies have revealed evidence which shows significant reduction in mortality among HIV co-infected tuberculosis patients who are appropriately initiated on antiretroviral therapy during the course of tuberculosis treatment (Karim et al, 2010).

The results of this study showed that the starting of ART during tuberculosis therapy in patients with confirmed HIV/Tuberculosis co-

infection reduced mortality by 56% and that a delay in initiating Antiretroviral therapy increased the death rate from 6.5 per 100 person-years to 14.5 per 100 person-years when the initiation of ART was delayed until the completion of ATT. It was also noted that the interval between the end of the anti tuberculosis treatment and the starting of ART is important, because a significant number of deaths in the sequential therapy group occurred during this period.

A study conducted in a rural province in THAILAND expressed that decrease in the risk of death during ATT for patients receiving Antiretroviral therapy(Akksilp et. al., 2007). A similar population-based study was conducted across four provinces in Thailand between October 2004 and March 2006 (Sanguanwongse, 2008). The results of the study indicated that only11% of TB/HIV co-infected patients started on ART died compared to 46% of the co-infected patients for whom ART was not prescribed. Even for those with very low CD4 counts (<10cells/ml) 21% of the patients receiving ART died, compared with 81% of those not receiving ART. Sanguanwongse (2008) concluded that the risk of death among HIV co-infected TB patients who were not receiving ART was six times greater than the risk of death among HIV co-infected TB patients receiving ART in the resource-limited public health setting in Thailand.

The literature reviewed suggests that both single site-based and population-based studies provide evidence which shows that the appropriate initiation of Antiretroviral therapy during anti tuberculosis therapy significantly reduces mortality among HIV Tuberculosis co-infected patients.

FACTORS INFLUENCING THE INITIATION OF ART DURING TB TREATMENT

The combination of antiretroviral therapy with tuberculosis treatment results in a rapid reduction in the incidence of other opportunistic infections, because ART restores pathogen- specific immune responses (Lawn, 2009). Despite all the evidence supporting the concomitant treatment of both diseases in HIV/TB co-infected patients, ART is often deferred in co-infected patients, sometimes until the completion of ATT, due to potential drug interactions between rifampicin and some classes of ART drugs, IRIS, the overlapping side-effects of TB drugs and antiretroviral drugs, the high pill burden, and programmatic challenges (Karim et. al., 2010)Concurrent administration of ART and TB medicines is complicated by the overlapping side-effects of both therapies and the fact that rifamycins (rifampicin, rifapentine, rifabutin) tend to decrease the serum levels of non-nucleoside reverse transcriptase inhibitors and protease inhibitors. Thus, the simultaneous

administration of these medicines needs meticulous drug selection, dose modifications and close therapeutic drug monitoring (Lawn, 2009).

The problem of patients refusing ART is not unique to one country. Maisels (2004) reported that 57% of eligible patients who did not receive ART declined this intervention when it was recommended by the provider following a review of medical records at a Community Health Centre in the USA, with the aim of determining the reasons why certain eligible patients did not receive ART between 1997 and 1998.

Reasons for declining

1. ART were not being ready for strict adherence to a complex regimen (7 of 16)
2. Fear of the side effects (6 of 16).
3. Active drug use, religious beliefs, homelessness, confidentiality concerns
4. Depression and feeling well without HAART
5. Homelessness, depression.

The total distance travelled by patients to an ART site and the cost of the transport involved have also been proven to have an influence on the acceptance of antiretroviral therapy among TB patients co-infected with HIV.A study of HIV/TB co-infected patients whose participants were drawn from Zambia and South Africa also showed (Bond et. al., 2009).

The required expenditure on transport in relation to the distance travelled to reach the healthcare facility was not affordable for some patients , resulting in either a late or a failure to initiate Antiretroviral therapy. However, antiretroviral therapy was more readily available for households of low socio-economic status because of the shorter distances travelled to health facilities, the availability of disability grants, and their less absolute poverty. Travelling long distances to health facilities also proved to be a limitation on the availability of ART in the rural parts of the Eastern Cape Province in South Africa (Bond et. al., 2009).

TREATMENT OF HIV-TB CO-INFECTION

Since the world health organisation declared in 1993 that Tuberculosis was a global emergency, the Directly Observed Treatment Short course strategy has been the key public health intervention that has been widely used to affect global Tuberculosis control [70]. Improved

survival rate and Tuberculosis outcome in ART treating patients [71,72]. In addition, ART decreases Tuberculosis rates

1. By 90% at an individual level
2. By 60% at a population level
3. It reduces TB recurrence rates by 50% .

Immuno-pathological reactions, termed "the immune reconstitution Inflammatory syndrome" (IRIS), occur most commonly when ART is initiated in patients with tuberculosis (paradoxical Tuberculosis-associated IRIS), or in which HAART therapy results in new presentation of previously undetected (likely subclinical) TB infection (unmasking TB-associated IRIS). Reports estimating the prevalence of TB-IRIS in patients with undergoing new ARVs are variable, ranging from as low as 7.6% in one to as high as 32%. **Clinically it manifests as fever and coarsening or appearance of pulmonary infiltrates, lymphnode enlargements, serous cavity effusions or intracranial tuberculomas, subcutaneous abscess in patients with miliary TB, rarely acute respiratory syndrome(ARDS) and acute renal failure can develop.** It usually develops after 6 weeks of course of ART. However ATT and HAART need to be continued without interruption.

First-line HAART regimen should contain two NRTIs plus one NNRTI . The ideal NRTI is zidovudine or tenofovir combined with either lamivudine or emtricitabine. For the NNRTI, efavirenz preferred over nevirapine due to fewer adverse reactions. **According to WHO Anti tuberculosis treatment should initiated before Antiretroviral therapy**. Antituberculosis treatment should be started immediately who is already on ART and HAART needs to be revised to prevent possible drug-drug interactions In all HIV tuberculosis co-infection patients, co-trimoxazole preventive therapy (CPT) for pneumocystis jiroverci should be started and continued throughout anti tuberculous treatment . CPT substantially decreases death rate in HIV-positive TB patients .Treatment strategies HIV TUBERCULOSIS co infection:

1. Pulmonary Tuberculosis with CD4 count <50cells/µl or extra

   Pulmonary TB – start ART immediately following ATT

2. Pulmonary Tuberculosis with CD4 count 50-200cells/µl - start ART after 2 months of ATT
3. Pulmonary tuberculosis with CD4 count >200 cells/µl –treat tuberculosis start ART after completion of anti tuberculosis treatment

CHALLENGES OF DIAGNOSING AND TREATING TUBERCULOSIS AND HIV

The first challenge of diagnosing TB lies in the fact that a sizeable proportion of patients in countries with high TB incidence do not seek medical attention for their symptoms early enough. A high proportion of those who choose to seek medical care do so late in the natural history of the disease. TB in many cases has an insidious onset with initially few non specific symptoms so that patients may seek care late and the health care workers for the same reason may not think of TB when the patient presents. The primary method, sputum smear examination, currently used most for diagnosing TB in low resource-limited settings has limited sensitivity; the patient may visit the TB diagnostic facility several times before achieving a diagnosis of TB.

Assessing diagnostic delay in HIV disease is a bit more difficult due to the long latency Period and the subtle and insidious onset of the disease symptoms that can stretch for several Months or even several years. Most HIV infections are symptomless until quite substantial immunological damage has occurred. In terms of diagnostic delay, 40% or more of HIV infected patients have advanced disease at the time of HIV diagnosis. A study carried out in two tertiary hospitals in Uganda, showed that although HIV test uptake was high at 98% among admitted

patients, 81% of these patients were being tested for HIV infection for the first time. Among patients who were tested for HIV during hospitalization in an urban tertiary hospital, 64% turned out to be HIV infected. Waiting to be tested for the first time for HIV infection until admission in a tertiary institution means a quite substantial delay. Additional challenges are present regarding the optimal timing for starting of combination ART in patients co-infected with Tuberculosis.

The second challenge in the diagnosis and treatment of these two diseases is getting people to take diagnostic tests and get test results. The success of any TB (and possibly to some extent HIV) control programme lies in detecting the cases and starting eligible patients on good quality treatments. In primary health care programmes it is crucial that HIV patients are diagnosed early in their disease process to avoid challenges of deciding when to start treatments in the setting of co-infections and vice versa. Moreover cART reduces mortality among TB patients. Despite the adoption by many countries of the WHO provider initiated HIV testing and counseling guidelines, uptake of HIV testing is still low in outpatient departments, also among TB patients. A study in Ethiopia found missed opportunities for HIV diagnosis in 52% of patients.

The third challenge in the TB and HIV treatment programmes is to maintain those patients on treatment who have initiated therapy. High defaulting levels from anti-tuberculosis treatment (range 11-30%) have been reported in Africa. Similar to what is seen in TBtreatment, between 16% to 26% on cART have been lost to follow-up within three years of starting cART in resource-limited settings.

Data concerning defaulting or loss to follow up from ART programmes are still limited. The fourth challenge in treating TB and HIV diseases is the poor adherence to treatments among those patients who do not abandon their treatments. Despite the high adherence levels reported for patients who remain on their cART or TB treatments, a sizeable proportion of patients adhere poorly to their treatments. Importantly, the on-and-off interruptions in medications result in drug resistance. Good adherence to TB treatment is essential for cure from the disease and plays a crucial role in TB control.

Similarly, good adherence to cART is critical for achieving viral suppression and good clinical outcomes.

STUDIES IN PATIENTS WITH CO-INFECTION

A study conducted in Portugal to assess factors of an poor Tuberculosis outcome (no cure or death) and to assess factors of non-adherence in HIV positive TB patients on ART, showed that 32.9% of patients were non-adherent to treatment and that 22.9% had an unfavorable outcome. Non-adherence was found to be the only predictor of an unfavorable outcome and adherence was independently associated with I.V. drug use, treatment complications and use of methadone.

In this study, the sample size was small (70 patients), and the timing of ART initiation was not mentioned [73].A retrospective cohort study done in England to assess the benefits ,risks of administering ART during the treatment of Tuberculosis in HIV infected patients showed that there was a significant decrease in viral load and AIDS defining illness in those who were initiated on ART, as well as a decrease in mortality. In addition, there was a Significant association between the occurrences of adverse events and use of ART.10% of patients had paradoxical worsening, 90% of whom were on ART. The authors point out the fact that the occurrence of AE could potentially influence adherence to either disease but there was no evidence of it in the study [74].

A study conducted in Malawi to assess whether Antiretroviral therapy reduces case fatality in HIV positive patients with TB, in which

patients who received Antiretroviral therapy in the continuation phase of anti tuberculosis treatment were compared to those who didn't receive Antiretroviral therapy showed that ART started in the continuation phase didn't have any effect in reducing case fatality (6 out of ten deaths occur in the intensive phase).Similarly, the other treatment outcomes were also similar in the two groups e.g. treatment success, loss to follow up, although that was not discussed by the authors. The limitation in this study is that the two groups compared were patients who accepted and those who refused ART, hence there might be differences in economic or social status between the groups which influenced treatment outcome [75]

Another study was also conducted in Malawi to compare 6-month and 12-month cohort treatment outcomes of HIV positive Tuberculosis patients and HIV positive non Tuberculosis patients treated with Anti retroviral therapy , and this study revealed that those people with TB had a significantly lesser default rate and the authors discussed that it was possibly due to the fact that these patients had time to stabilize and prepare for their ART since they were started on Antiretroviral therapy only in the continuation phase of anti tuberculosis treatment, whereas the other patients were started on anti retroviral therapy in a short time [76]. Thus, this can indicate that adherence to either treatment (anti-TB or

ART) might be a challenge for those patients who initiate the anti retroviral therapy drugs in the intensive phase of anti-tuberculosis treatment. A study conducted in Nigeria to compare the outcomes of HIV –TB Positive and HIV -TB negative patients showed that default rate, which was 17% overall was not significantly related to Human immuno deficiency status, although more Human immunodeficiency positive than Human immunodeficiency negative patients defaulted from treatment. It was also found that reasons for default to TB treatment in the HIV positive patients included: severely ill patients going back their home town to receive support from their extended families; patients leaving the area to consult healers that advertised that they would cure HIV; seriously ill patients not being able to come to collect their drugs personally; stigma and discrimination forcing some HIV positive patients to relocate, mainly those with HIV wasting and other obvious HIV related symptoms. The study showed a significant difference in mortality (15.5%in HIV positives VS 3.1% in HIV negatives.)The HIV positive patients were not on ART in this study [77].

Two studies conducted in England also showed that paradoxical reactions during TB treatment were more common in co-infected patients receiving ART, mainly when introduced early [78]; adverse events also occurred more frequently in Human immunodeficiency virus positive

patients in one study comparing Human immune deficiency negative patients with HIV positive patients (of whom 70% received ART).But despite a higher rate of serious side effects such as persistent vomiting, rash, hepatotoxicity, peripheral neuropathy, in the HIV positive individuals, TB treatment discontinuation was similar in the two groups [79].

Two studies on adherence to TB preventive therapy in HIV positive patients showed high rates of default. 26.5% of patients defaulted from preventive treatment in Thailand, with migration for job search, denial of HIV status, perceived drug side effects, and confusion about the duration of treatment being associated with defaulting. Married people, women, outpatients, surviving spouses, the self-employed, and those with no history of physical symptoms were more likely to be adherent to the treatment [80].Similarly in South Africa, more than half of HIV patients initiated on TB preventive treatment interrupted it. [81].

RCT SHOWING SURVIVAL BENEFITS OF EARLY ANTI RETROVIRAL THERAPY INITIATION

Karim et al. (2010) conducted the trial in Durban , South Africa "Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPIT)" . They identified the patients with CD4 counts lower than five hundred cells per Litre, death rate was lower for patients assigned to start ART while on TB treatment than for those who were assigned to complete TB treatment before initiating ART.

This result held true in subsets of patients with CD4 counts above and below 200 cells/_L. Although the incidence of TB-associated IRIS was higher amongst patients assigned to initiate ART while on TB treatment, no deaths were attributable to TB-associated IRIS. No difference was found in the proportions of patients being diagnosed with grade 3 or 4 adverse events (other than IRIS).Philpott and Schuklenk (2010); Wilson and Meintjes (2010) and Boulle et al.(2010a) critiqued the study by Karimet al. (2010), saying that People with HIV infected with CD4 T cell count less than 200 cells/ul should not have been randomized to receiving ART after ATT completed. They argued that it was predictable based on prior observational studies that patients with CD4T cell counts less than 200 cells/Ul would have increased mortality if they only started ART after TB treatment rather than during TB treatment.

In addition, the 2004 South African ART guidelines (in force at the start of the SAPIT trial) recommended that patients having tuberculosis with CD4 count less than 200 cells/l should start anti retroviral therapy after completing 2 months of anti tuberculosis treatment (or after completing two weeks and as soon as they are tolerating anti tuberculosis treatment if the patients CD4 counts were below 50cells/_L).

Cohen (2010), however, reports some clinicians and public health officials as saying that the criticism by Philpott and Schuklenk (2010) was too negative and that the results from this study would be helpful in assuring clinicians that starting Anti retroviral therapy during treatment for tuberculosis treatment does significantly reduce mortality. The SAPIT study also included a comparison of patients starting Anti retroviral therapy within the one month of Tuberculosis treatment(early ART), versus within one month of the continuation phase of Tuberculosis treatment (late ART). Karim et al. (2011) found an increased risk of IRIS (Incidence-Rate Ratio (IRR) 2.62, 95% CI: 1.48-4.82) and of switching antiretroviral drugs as a result of adverse events (10 versus 1, $p = 0.006$) for patients receiving early ART compared to late ART, but no overall AIDS-free survival benefit ,The median CD4 count was 150 cells/_L and did not differ between groups.

In a subset of patients with CD4 cell counts lower than50 cells/_L however, Karim et al. (2011) found a reduction in the combined incidence of AIDS or death (IRR 0.32, 95% CI: 0.07-1.13) that they suggest outweighs the risks of IRIS (IRR 4.71, 95% CI: 1.48-19.64) and the need to switch ART because of side effects (3 versus 0 patients) for patients starting ART earlier versus later with respect to the time they started TB treatment.

Another randomized controlled trial comparing mortality among Patients with differing times of starting ART after starting antituberculosis treatment was performed by Blanc et al. (2011) among HIV positive Cambodian patients. This study only included patients with CD4 counts lower than 200 cells/_L that had a Tuberculosis diagnosis confirmed by a AFB smear positivity Blanc et al. (2011) found that patients initiating ART two weeks after starting TB treatment had a lower hazard of death than those starting ART eight weeks after the start of anti tuberculosis treatment. Since median CD4 count for all patients was very low (25 cells/_L) this result is consistent with that of Karim et al. (2011).A third study that investigated the optimal timing of initiating ART during TB treatment was conducted by Havlir et al. (2011).

They enrolled patients from four continents who had confirmed or probable TB diagnoses and CD4 counts lower than 250 (median 77) cells/_L. There are decreased proportion of patients dying or experiencing a previously undiagnosed Event that indicates AIDS in the subset of patients with CD4 counts lower than fifty cells/L (15.5% versus 26.6%, 95% CI: 1.5-20.5) for Early group (within 2 weeks of initiating treatment for TB) versus later (8-12 weeks after initiating treatment for TB).

For patients with CD4 cell counts of 50 cells/_L or greater, the difference in proportions of patients dying and experiencing AIDS-defining events was not statistically significant (p 0.67) for those starting ART earlier versus later. Havlir et al. (2011) did find an increased proportion of patients being diagnosed with TB-associated IRIS in the earlier ART compared to the later ART group (11% versus 5%, p =0.002), but no deaths were attributed to TB-associated IRIS.

There is no significant difference in drug toxicity or Laboratory abnormalities in patients who started ART earlier versus later. Despite the greater risk of patients developing IRIS and needing to switch antiretroviral drugs as a result of toxicity, all three studies {Havlir et al, Karim et al,Blanc et al} are in agreement that early ART initiation (two

to four weeks after starting TB treatment) is associated with lower mortality for patients having very low CD4 counts (lower than 50 cells/_L or a median of 25 cells/_L)

METHODOLOGY

MATERIALS AND METHODS

SOURCE OF DATA

This study was conducted at Mahatma Gandhi Memorial Government Hospital ,Trichy in collaboration with ART CENTRE in our institution .

STUDY DESIGN

Unicentric prospective comparative study

PERIOD OF STUDY

January 2013 to September 2014

ETHICS COMMITTEE APPROVAL

Approval was obtained from Institutional ethics committee.

INCLUSION CRITERIA

- Age > 18
- Documented history of HIV-TB co-infection in Out-patient or inpatient
- Consent to the study

EXCLUSION CRITERIA

- Age <18
- Diabetic, chronic renal disease, Known case of hypertension
- Patients who are already on ART now diagnosed to have Tuberculosis

CONSENT

Informed consent was obtained from the patient in both groups

METHOD

HIV -TB co-infected individuals on ATT are entered into the groups early (2-8 weeks) and delayed(>8weeks) according to time of presentation. All patients were thoroughly examined and basic investigations were taken categorised according to RNTCP guidelines and started on ATT. NACO provided the antiretroviral drugs free of cost. Patients followed for 12 months regarding side effects, IRIS,TB outcome, HIV progression,CD4 count.

RESULTS

RESULTS

FREQUENCY TABLE

TABLE 1.AGE

Particulars	No. of respondents (n=60)	Percentage (100%)
Below 20yrs	2	3.3
21-30Yrs	9	15
31-40yrs	23	38.3
Above 40yrs	26	43.3

FIG 1.AGE

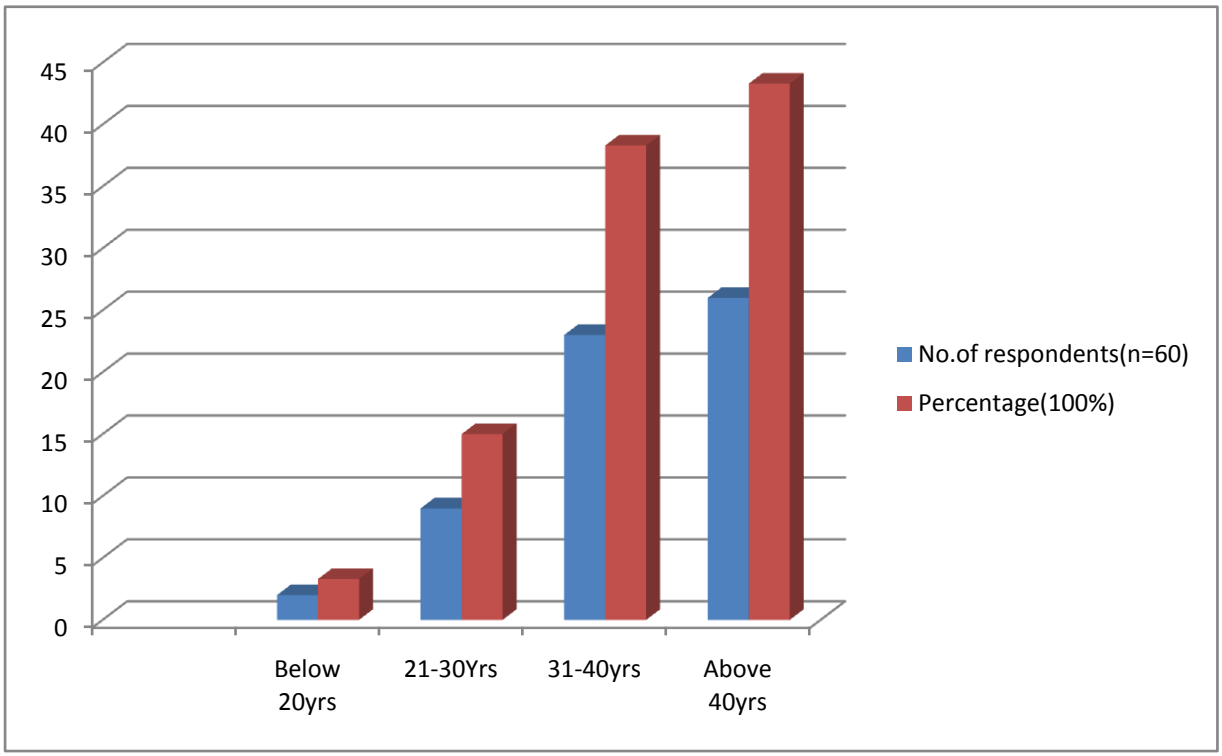
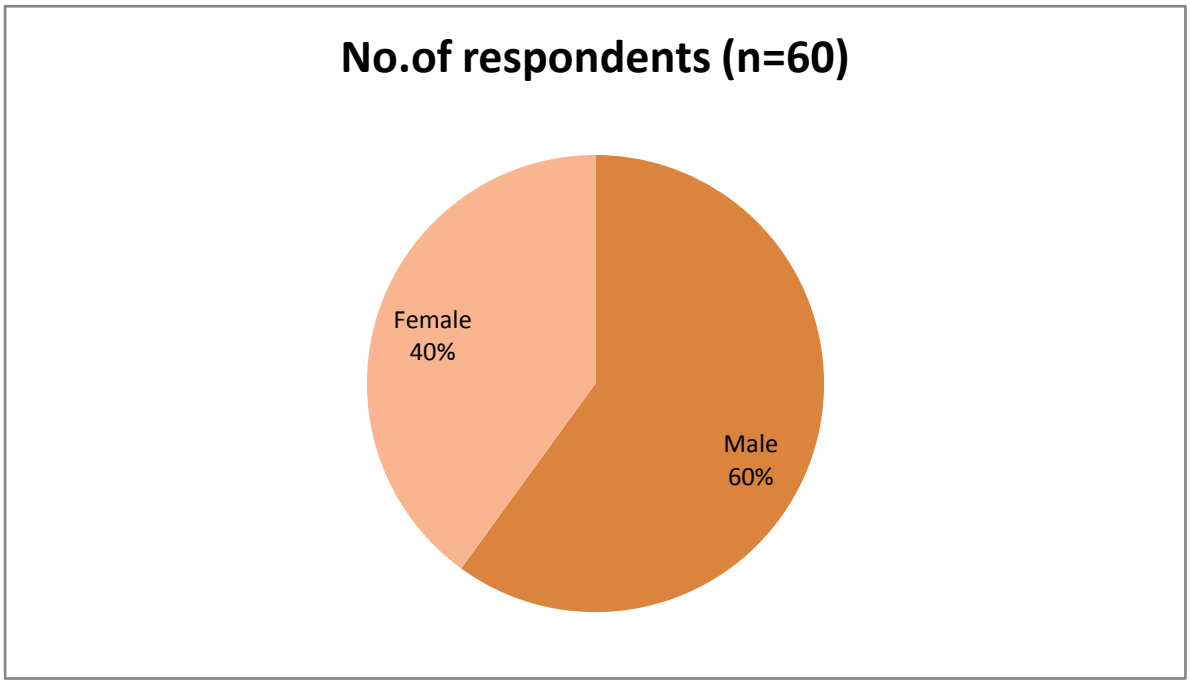

45
40
35
30
25
20
15
10
5
0
Below 20yrs
21-30Yrs
31-40yrs
Above 40yrs
No.of respondents(n=60)
Percentage(100%)

TABLE 2.SEX

Particulars	No. of respondents (n=60)	Percentage (100%)
Male	36	60.0
Female	24	40.0

FIG 2.SEX



TAB.3.INTERVEVAL BETWEEN ART AFTER ATT

Particulars	No. of respondents (n=60)	Percentage (100%)
2 to 8 weeks	30	50.0
More than 8 weeks	30	50.0

TAB.4. TUBERCULOSIS TREATMENT CATEGORY

Particulars	No. of respondents (n=60)	Percentage (100%)
CAT-1	58	96.7
CAT-2	2	3.3

TAB.5 . IRIS

Particulars	No. of respondents (n=60)	Percentage (100%)
Nil	56	91.6
Fever	2	3.3
INC NODE	1	1.7
INC PLU	1	1.7
INC PUL	1	1.7

FIG.3. IRIS

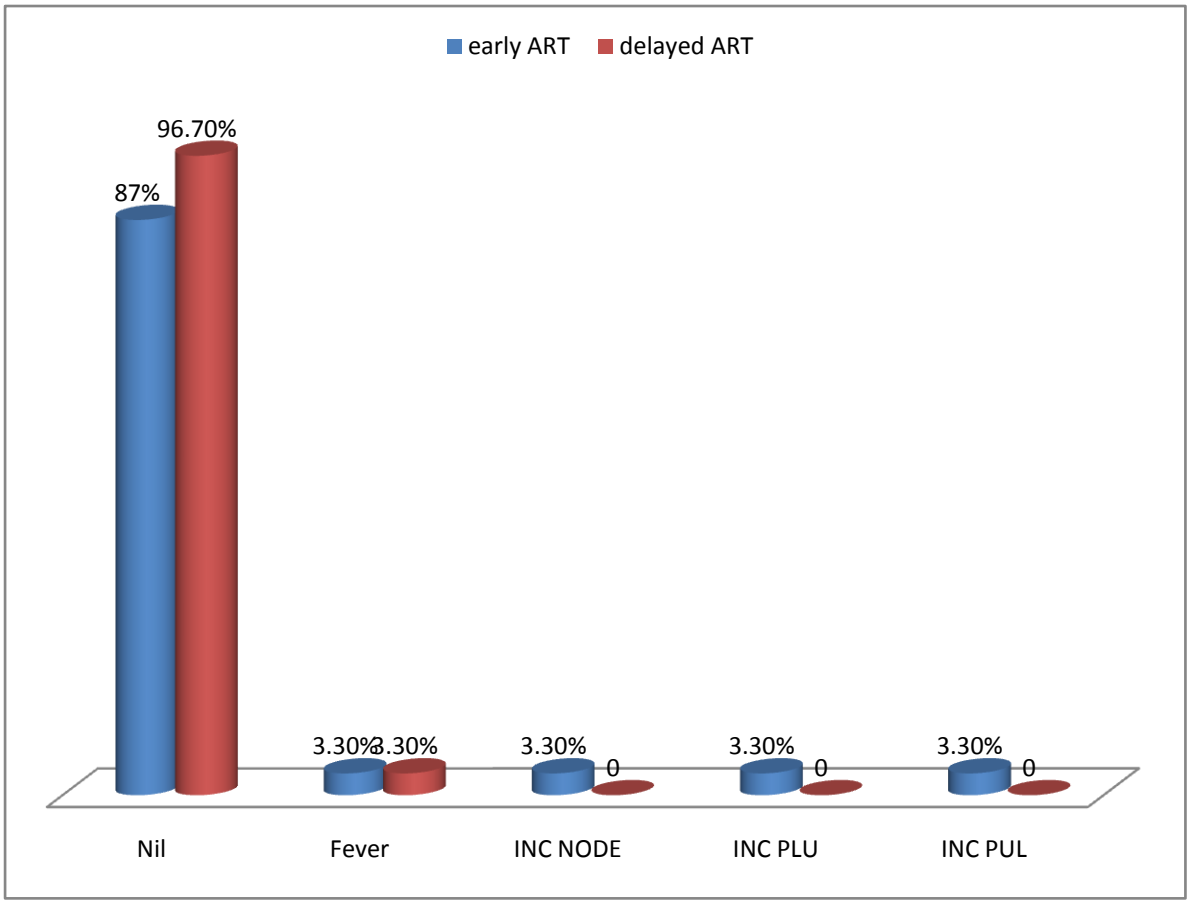

early ART
delayed ART
96.70%
87%
3.30%
3.30%
3.30%
0
3.30%
0
3.30%
0
Nil
Fever
INC NODE
INC PLU
INC PUL

TABLE 6..HB

Particulars	No. of respondents (n=60)	Percentage (100%)
Less than 8	5	8.3
More than 8	55	91.7

TABLE 7.SITE OF TB

Particulars	No. of respondents (n=60)	Percentage (100%)
EXTRA PULMONARY TB	6	10.0
PULMONARY TB	54	90.0

FIG 4.SITE OF TB

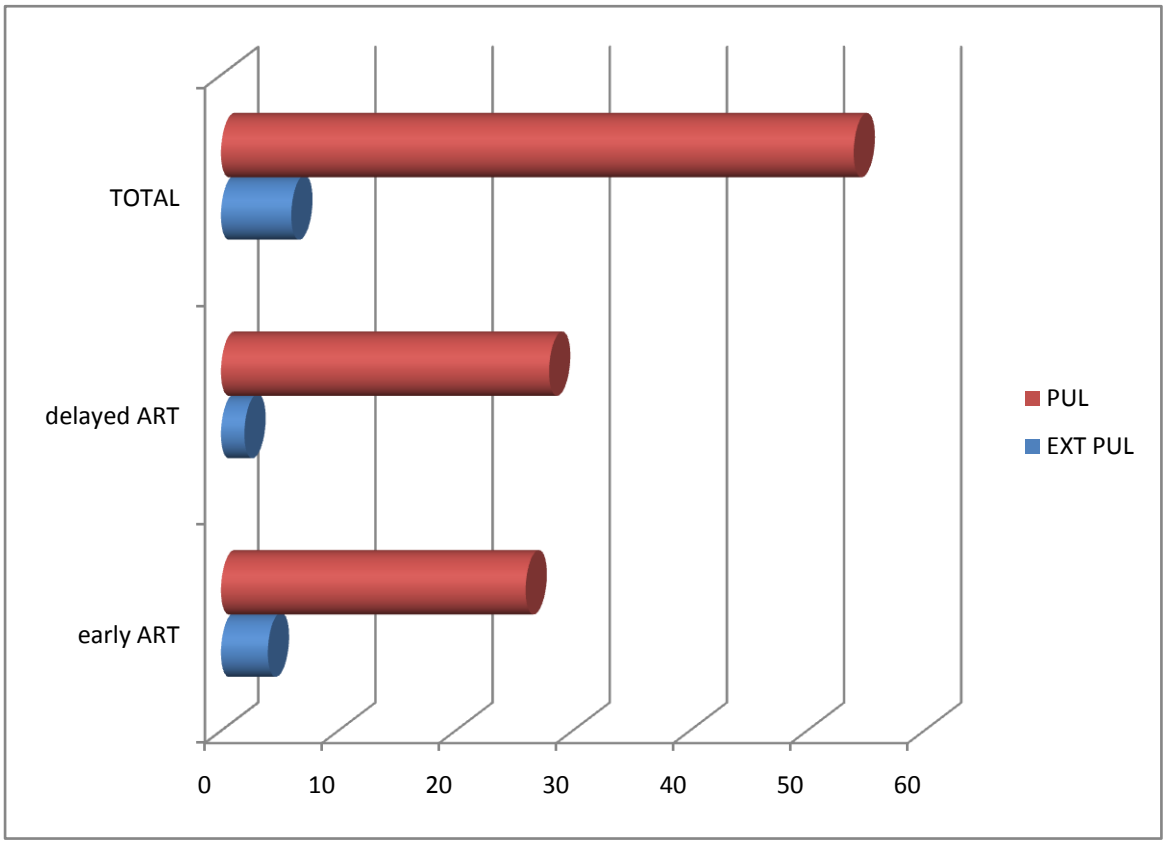


TABLE 8. SPUTUM

Particulars	No. of respondents (n=60)	Percentage (100%)
NO SPUTUM	6	10.0
AFB NEGATIVE	49	81.7
AFB POSITIVE	5	8.3

TABLE 9.ADVERSE EFFECTS

Particulars	No. of respondents (n=60)	Percentage (100%)
Nil	57	95.0
Anemia	1	1.7
Hepatitis	2	3.3

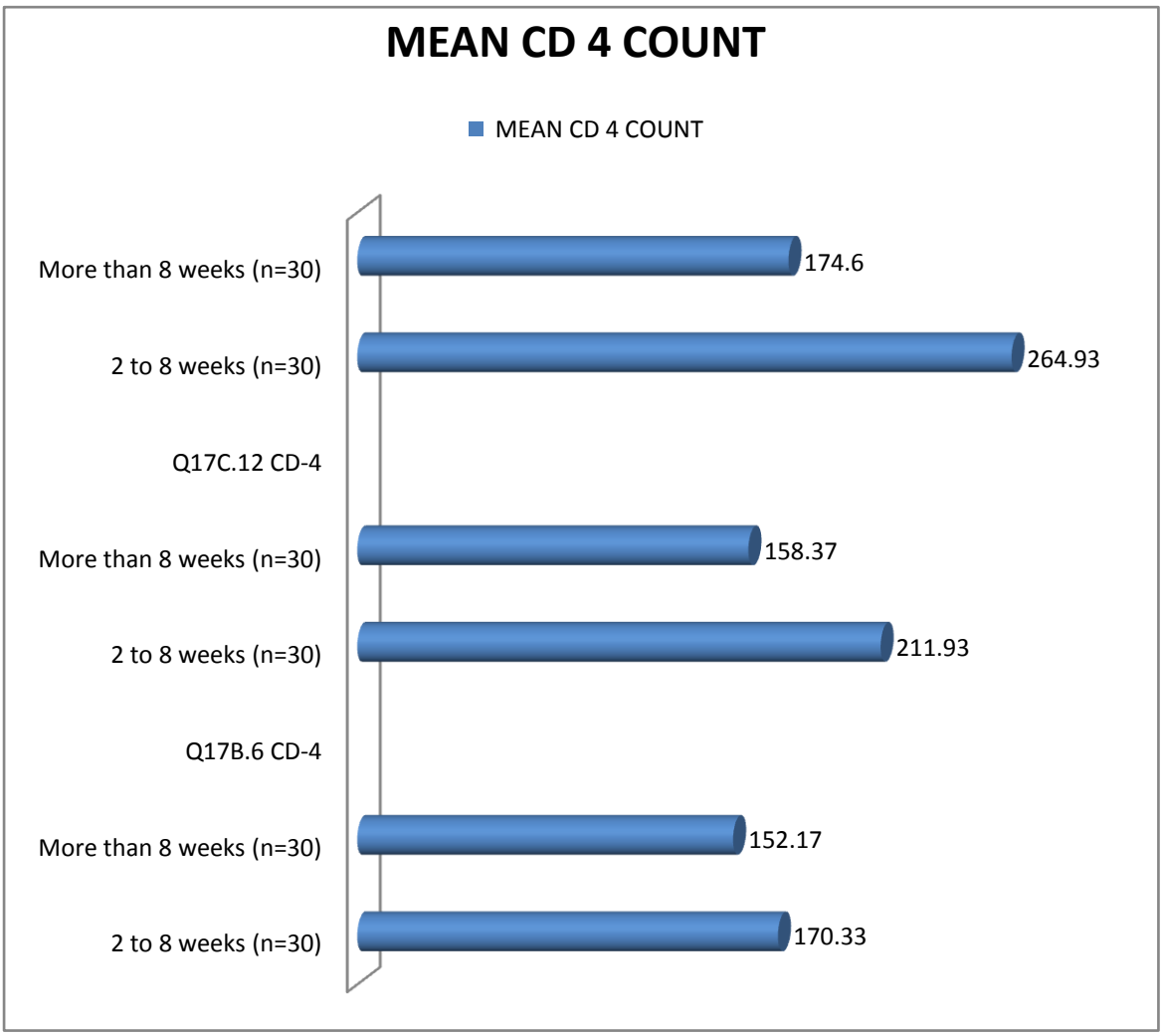
TABLE 10.OUTCOME

Particulars	**No. of respondents (n=60)**	**Percentage (100%)**
Complete	58	96.7
Died AFT	2	3.3

Table 11, Mean CD4 count in early and delayed ART groups

Q17A.B CD-4	MEAN CD 4 COUNT
2 to 8 weeks (n=30)	170.33
More than 8 weeks (n=30)	152.17
Q17B.6 CD-4	
2 to 8 weeks (n=30)	211.93
More than 8 weeks (n=30)	158.37
Q17C.12 CD-4	
2 to 8 weeks (n=30)	264.93
More than 8 weeks (n=30)	174.6

FIG 5, Mean CD4 count in early and delayed ART groups



DESCRIPTIVE STATISTICS

Item	Min	Max	Mean	S.D
Q2.AGE	18	58	39.05	9.615
Q7.DUR	2	16	6.67	3.620
Q10.HB	6.10	13.00	9.8983	1.29830
Q11.TC	3658	10456	6778.27	1880.770
Q12A.ESR	13	100	43.72	20.804
Q12B.ESR	21	150	57.85	25.311
Q13.B.UREA	20	55	37.85	6.351
Q14.S.CREAT	.40	1.80	.8647	.31973
Q15.A LIVER ENZYMES (AST)	25	59	40.93	7.974
Q15.B LIVER ENZYMES (ALT)	25	62	39.98	7.626
Q15.C.2 LIVER ENZYMES (AST)	30	112	43.77	14.269
Q15.D LIVER ENZYMES (ALT)	29	234	45.32	29.034

Q15.E.4 LIVER ENZYMES (AST)	30	130	43.78	18.700
Q15.f.4 LIVER ENZYMES (ALT)	29	150	42.60	18.161
Q17A.B CD-4	53	310	161.25	71.190
Q17B.6 CD-4	52	486	185.15	87.320
Q17C.12 CD-4	80	646	219.77	112.633

T-Test

	Mean	**S.D**	**Statistical Inference**
Q2.AGE			
2 to 8 weeks (n=30)	39.33	7.689	T=.226 df=58 .822>0.05 Not Significant
More than 8 weeks (n=30)	38.77	11.349	
Q7.DURATION			
2 to 8 weeks (n=30)	3.40	1.221	T=-16.706 df=58 .000<0.05 Significant
More than 8 weeks (n=30)	9.93	1.760	
Q10.HB			
2 to 8 weeks (n=30)	10.0233	1.44023	T=.743 df=58 .461>0.05 Not Significant
More than 8 weeks (n=30)	9.7733	1.15009	
Q11.TC			
2 to 8 weeks (n=30)	6747.93	1800.788	T=-.124 df=58 .902>0.05 Not Significant
More than 8 weeks (n=30)	6808.60	1987.921	
Q12A.ESR			
2 to 8 weeks (n=30)	43.57	22.295	T=-.055 df=58 .956>0.05 Not Significant
More than 8 weeks (n=30)	43.87	19.581	

Q12B.ESR			
2 to 8 weeks (n=30)	56.70	25.115	T=-.349 df=58 .728>0.05 Not Significant
More than 8 weeks (n=30)	59.00	25.882	
Q13.B.UREA			
2 to 8 weeks (n=30)	36.53	5.740	T=-1.628 df=58 .109>0.05 Not Significant
More than 8 weeks (n=30)	39.17	6.747	
Q14.S.CREATININE			
2 to 8 weeks (n=30)	.8193	.28292	T=-1.100 df=58 .276>0.05 Not Significant
More than 8 weeks (n=30)	.9100	.35170	
Q15.A LIVER ENZYMES (AST)			
2 to 8 weeks (n=30)	39.03	8.704	T=-1.885 df=58 .064>0.05 Not Significant
More than 8 weeks (n=30)	42.83	6.793	
Q15.B LIVER ENZYMES (ALT)			
2 to 8 weeks (n=30)	38.70	8.643	T=-1.311 df=58

More than 8 weeks (n=30)	41.27	6.341	.195>0.05 Not Significant
Q15.C.2 LIVER ENZYMES (AST)			
2 to 8 weeks (n=30)	45.07	19.104	T=.703 df=58 .485>0.05 Not Significant
More than 8 weeks (n=30)	42.47	6.766	
Q15.D LIVER ENZYMES (ALT)			
2 to 8 weeks (n=30)	48.90	40.381	T=.955 df=58 .343>0.05 Not Significant
More than 8 weeks (n=30)	41.73	7.602	
Q15.E.4 LIVER ENZYMES (AST)			
2 to 8 weeks (n=30)	46.43	25.561	T=1.100 df=58 .276>0.05 Not Significant
More than 8 weeks (n=30)	41.13	6.601	
Q15.f.4 LIVER ENZYMES (ALT)			
2 to 8 weeks (n=30)	44.37	25.091	T=.751 df=58 .456>0.05 Not Significant
More than 8 weeks (n=30)	40.83	5.919	
Q17A.B CD-4			

2 to 8 weeks (n=30)	170.33	77.064	T=.988 df=58 .327>0.05 Not Significant
More than 8 weeks (n=30)	152.17	64.815	
Q17B.6 CD-4			
2 to 8 weeks (n=30)	211.93	101.137	T=2.477 df=58 .016<0.05 **Significant**
More than 8 weeks (n=30)	158.37	61.640	
Q17C.12 CD-4			
2 to 8 weeks (n=30)	264.93	133.098	T=3.367 df=58 .001<0.05 **Significant**
More than 8 weeks (n=30)	174.60	62.243	

Tables

	Q7.DUR			Statistical inference
	2 to 8 weeks (n=30)	**More than 8 weeks (n=30)**	**Total (n=60)**	
Q2.AGE				
Below 40yrs	19(63.3%)	15(50%)	34(56.7%)	X^2=1.086 df=1 .297>0.05 Not Significant
Above 40yrs	11(36.7%)	15(50%)	26(43.3%)	
Q3.SEX				
Male	20(66.7%)	16(53.3%)	36(60%)	X^2=1.111 df=1 .292>0.05 Not Significant
Female	10(33.3%)	14(46.7%)	24(40%)	
Q8.TB RX				
CAT-1	28(93.3%)	30(100%)	58(96.7%)	X^2=2.069 df=1 .150>0.05 Not Significant
CAT-2	2(6.7%)	0	2(3.3%)	
Q9.IRIS				
Nil	26(87%)	29(96.7%)	55(91.7%)	X^2=2.071 df=3 .344<0.05 Not Significant
Fever	1(3.3%)	1(3.3%)	2(3.3%)	
INC NODE	1(3.3%)	0	1(1.7%)	
INC PLU	1(3.3%)	0	1(1.7%)	

INC PUL	1(3.3%)	0	1(1.7%)	
Q10.HB				
Less than 8	3(10%)	2(6.7%)	5(8.3%)	X^2=.218 df=1 .640>0.05 Not Significant
More than 8	27(90%)	28(93.3%)	55(91.7%)	
q18.SITE				
EXTRA PULMONARY TB	4(13.3%)	2(6.7%)	6(10%)	X^2=.741 df=1 .389>0.05 Not Significant
PULMONARY TB	26(86.7%)	28(93.3%)	54(90%)	
q19a.B SPUTUM				
NO SPUTUM	4(13.3%)	2(6.7%)	6(10%)	X^2=2.977 df=2 .226>0.05 Not Significant
AFB NEGATIVE	22(73.3%)	27(90%)	49(81.7%)	
AFB POSITIVE	4(13.3%)	1(3.3%)	5(8.3%)	
Q19b.2 SPUTUM				
NO SPUTUM	26(86.7%)	28(93.3%)	54(90%)	X^2=.741 df=1 .389>0.05 Not Significant
AFB NEGATIVE	4(13.3%)	2(6.7%)	6(10%)	

q19c.6 SPUTUM				
NO SPUTUM	26(86.7%)	28(93.3%)	54(90%)	X^2=.741 df=1 .389>0.05 Not Significant
AFB NEGATIVE	4(13.3%)	2(6.7%)	6(10%)	
q20.A/E				
Nil	28(93.3%)	29(96.7%)	57(95%)	X^2=3.018 df=2 .221>0.05 Not Significant
Anaemia	0	1(3.3%)	1(1.7%)	
Hepatitis	2(6.7%)	0	2(3.3%)	
q21.outcome				
Completed	29(96.7%)	29(96.7%)	58(96.7%)	X^2=.000 df=1 1.000>0.05 Not Significant
Died after ATT	1(3.3%)	1(3.3%)	2(3.3%)	

DISCUSSION

DISCUSSION

This study was conducted to determine optimal time to initiate ART in HIV – TB co-infected patients on ATT. The study population was 60 adults presenting to MGMGH from the period JAN 2013 to SEP 2014.

AGE WISE DISTRIBUTION (TABLE 1)

of the total number of patients who presented with HIV TB Co – infection43.3% were in above 40 yrs of age group35.3% were in31-40yrs of age group15% belong to21-30yrs of age group Remaining 3.3% in less than 20 yrs of age group .20% 0f above 40 yrs of group were in early antiretroviral therapy group, remaining 23.3% were in late antiretroviral therapy. 25%of 31-40 yrs age group were in early ART group, remaining10.3% were in late ART group. 6.6% of 21-30 yrs age group were in early ART and 8.3% were in late ART group

SEX WISE DISTRIBUTION (TABLE 2)

60% (36 out of 60) of patients in this study were males, of these 33%(20 out of 60) were in early group, 27% (16 out of 60)were in late group.

40% (24 out of 60) of patients in this study were females, of these 17% (10 out of 60) were in early group, 23% (14 out of 60) were in late group.

ATT CATEGORY AND SITE OF TUBERCULOSIS (TABLE3&7)

In this study 58 patients were started on category 1Antituberculosis treatment, remaining 2 patients were started on category 2 (these 2 patients are under early group) . In 60 patients of this study only 6 patients had extra pulmonary tuberculosis. 2 out of 6 extra pulmonary Tuberculosis patients were in late group. Remaining 54 patients are pulmonary tuberculosis .

SPUTUM SMEAR EXAMINATION (TABLE 8)

Only 5 patients out of 54 patients with pulmonary tuberculosis had sputum smear positive. In extra pulmonary TB , lymphadenopathy was present in 2 cases, pleural effusion in 2 cases. Tuberculous meningitis & abdominal TB were the remaining subjects Even though 53 out of 60 patients had anaemia, but less than 8 gm present only in 5 patients. Only one patient HAD worsened anaemia after ART.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (TABLE 5)

In this study only 5 patients developed immune reconstitution inflammatory syndrome. Of these 4 patients were in early group. One patient was in late group. In this 5 patients , extra pulmonary tuberculosis was present in 2 subjects, pulmonary tuberculosis was present in 3 subjects. Only 1 out of 5 patients were started on CAT-2 ATT. Remaining 4 were started on CAT-1 ATT. Only one patient(early ART group) out of 5 patients with IRIS had hepatitis due to ATT. when compared early ART group patients had no significant increase in incidence of IRIS than late ART group patients. Although all 60 patients had completed ATT ,2 subjects (one from each group) died . There is no significant difference of mortality noted in both groups.

ADVERSE EFFECTS

Adverse effects of drug developed in 3 out of 60 patients. Two patients developed hepatitis. One had worsened anaemia. Two of these were in early group, one in late group. There was no significant difference of adverse effects noted in both groups.

CD4 COUNT (TABLE 11)

CD 4 count was done serially in every 6 months and compared in both groups. Mean of baseline CD4 count in early group is 170 Mean of baselineCD4 count in late group is 152. There is no significant difference of baseline CD4 count noted in both groups. Mean of 6 months CD 4 count in early group is 211. Mean of 6 months CD 4 count in late group is 158. There is significant difference of 6 months CD 4 count noted. P value is0.016 (less than 0.05). Mean of 12 months CD4 count in early group is 265 Mean of 12 months CD 4 count in late group is 174There is significant difference of 12 months CD4 count noted. P value is 0.001(less than 0.05).

Although there is rise in CD4 count serially , progressive increase was better in early ART group than late ART group . Since CD4 count is marker of immune dysfunction it indicates the progression of HIV.

Even though there is rise in CD4 count in both groups, but relatively there is increased CD4 count in early group than late group. HIV disease progression was slower in early ART group than in late ART group. So in this study even though there is high incidence of IRIS early ART group, HIV disease progression was slower in early group.

CONCLUSION

CONCLUSION

Before start of study, a written/ Informed consent was obtained from all the patients registered for the study, applying inclusion and exclusion criteria. DOTS given according to RNTCP category, Depending on the CD4 counts and WHO clinical staging ART was administered to all the patients.

Investigations were done initially and were repeated with each follow up. A specially designed proforma for each patient was made and the data collected likewise were transferred to a master chart. These results were subjected to the Statistical analysis. The study so completed revealed the following conclusions Our study revealed the male preponderance of 60% which is indicative of barriers preventing access to females to the ART. Grouping of patients with respect to age revealed that majority of subjects (43.3%) belonged to above 25-44 years age group which indicates that most patients affected by HIV/AIDS are in the sexually active group.

1. Increased incidence of IRIS in early ART group than delayed ART group but it is not significant
2. CD4 count was improved more in early ART group than delayed ART group
3. HIV disease progression is slower in early ART group than late ART group
4. No significant difference in mortality, tuberculosis outcome, adverse effects noted in among the two groups.
5. **In this study Even though there is increased incidence of IRIS in early ART group compared to delayed ART group, early ART initiation is preferred over delayed ART in view of delaying HIV disease progression.**

LIMITATIONS

LIMITATIONS

1. In this study ,60 patients were taken as sample size, Sample size was small
2. Quality of life , body mass index, disability grading, plasma viral load were not considered in this study
3. Duration of study was short, follow up needed for longer duration

SUMMARY

SUMMARY

1. Majority of patients were in the age group of above 40 years
2. Out of 60 people 60% were male, 40% were female
3. Most common form of tuberculosis was pulmonary tuberculosis(90%)
4. 8.3% were sputum smear positive
5. 3.3% were died during study period, shares by each group
6. 8.4% were developed IRIS, of these 6.7% in early group.
7. CD4 count even though increased in both groups, it is improved more in early group than late group

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BIBLIOGRAPHY

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ANNEXURES

PROFORMA

PROFORMA

NAME -

AGE/ SEX -

ADDRESS -

OCCUPATION -

INCOME -

ART REG NO. -

EDUCATION - Non literate/ Primary school, Secondary school, College & above

DATE OF REG. FOR ART -

DATE OF STARTING ATT -

DATE OF STARTING ART -

DURATION -

SOCIOECONOMIC STATUS -

COMPLAINTS -

H/O PRESENTING ILLNESS -

PAST HISTORY -

TREATMENT HISTORY -

GENERAL EXAMINATION -

CONSCIOUS

ORIENTED

FEBRILE / AFEBRILE

PALLOR ,ICTERIC, CYANOSIS,

CLUBBING

PEDAL EDEMA

GENERALISED LYMPHADENOPATHY

SYSTEMIC EXAMINATION -

CVS -

RS -

P/A -

CNS -

Time Period (months)	Hb %	TLC	DLC	ESR	B.Urea	Sr.Creatinine	S.Bil	ALT	AST	Blood Glucose	SPUTUM AFB	CD4 CELL COUNT	FNAC & BIOPSY	CXR PA VIEW
0														
3														
6														
12														

MASTER CHART

s.no	AGE/SEX	ART NO	ATT date	ART DATE	DUR	CAT	HB	LIVER ENZYMES(OT/PT)			CD-4			SITE	SPUTUM			A/E	outcome
								B	2	4	B	6	12		B	2	6		
1	40/M	5184	03.01.2013	10.02.2013	5 WK	CAT-1	10	25/27	30/30	32/30	207	389	400	PUL	N	-	-	NIL	COMPLETED
2	42/M	5265	11.02.2013	05.06.2013	15WK	CAT-1	9	36/30	38/30	40/30	148	200	300	PUL	N	-		NIL	COMPLETED
3	58/M	5244	02.02.2013	20.02.2013	2WK 4DA	CAT-1	10	30/30	35/32	33/30	75	75	100	PUL	N	-	-	NIL	COMPLETED
4	22/M	5296	20.02.2013	15.06.2013	15WK2DA	CAT-1	8	32/35	50/40	40/40	100	110	141	PUL	N	-	-	NIL	COMPLETED
5	25/F	5221	14.03.2013	15.04.2013	4WK	CAT-2	8	25/25	30/32	32/32	295	486	646	PUL	P	N	N	NIL	COMPLETED
6	41/M	5352	17.05.2013	25.07.2013	9WK 1DA	CAT-1	9.5	50/60	60/50	54/53	220	376	400	EXT PUL	-	-	-	NIL	COMPLETED
7	49/F	5293	17.02.2013	08.03.2013	2WK5DA	CAT-2	12	32/40	95/120	130/106	212	326	423	PUL	P	N	N	HEPATITIS	COMPLETED
8	37/M	5365	11.06.2013	25.06.2013	2 WK	CAT-1	8.9	50/35	38/39	40/37	195	286	143	PUL	N	-	-	NIL	COMPLETED
9	45/F	5354	15.03.2013	30.03.2013	2WK	CAT-1	10	34/43	39/43	47/42	197	198	432	PUL	N	-	-	NIL	COMPLETED
10	48/M	5331	15.03.2013	23.05.2013	8WK 4DA	CAT-1	9	54/50	40/34	36/37	95	120	214	PUL	N	-	-	NIL	COMPLETED
11	45/F	5582	08.03.2013	17.03.2013	2WK	CAT-1	9.4	38/32	34/36	38/37	102	123	265	EXT PUL	-	-	-	NIL	COMPLETED
12	46/F	5321	10.03.2013	26.05.2013	10WK2DA	CAT-1	8.2	35/36	37/32	38/34	228	228	347	PUL	N	-	-	NL	COMPLETED
13	20/M	5392	21.04.2013	28.06.2013	9WK	CAT-1	10	48/43	44/45	43/46	241	234	200	PUL	N	-	-	NIL	COMPLETED
14	52/M	5404	29.04.2013	29.05.2013	4 WK	CAT-1	12	42/26	39/30	37/39	221	234	250	EXT.PUL	N	-	-	NIL	COMPLETED
15	32/F	5873	24.4.2013	8.5.2013	2wk	CAT-1	10	32/33	42/38	39/34	53	151	410	PUL	N	-	-	NIL	COMPLETED
16	37/M	5365	28.6.2013	30.8.2013	8WK 2 DA	CAT-1	9.2	40/41	43/40	38/36	102	154	319	PUL	N	-	-	NIL	COMPLETED
17	43/M	5459	12.7.2013	15.9.2013	8WK 3DA	CAT-1	9.7	49/48	41/43	47/43	151	214	390	PUL	N	-	-	NIL	COMPLETED
18	36/M	5470	19.5.2013	10.07.2013	3WK	CAT-1	9.4	29/32	36/34	31/39	243	236	324	PUL	N	-	-	NIL	COMPLETED
19	50/M	5273	16.04.2013	30.4.2013	2WK	CAT-1	10	38/42	41/40	39/38	300	320	340	PUL	N	-	-	NIL	COMPLETED
20	34/M	5408	17.8.2013	20.09.2013	4WK 3DA	CAT-1	8.9	50/39	37/34	35/34	300	301	401	PUL	N	-	-	NIL	COMPLETED
21	35/M	5504	19.05.2013	10.08.2013	11WK 5DA	CAT-1	9.8	52/34	55/52	37/34	204	450	400	PUL	N	-	-	NIL	COMPLETED
22	40/M	4052	10.08.2013	31.08.2013	3WK	CAT-1	9.5	34/36	51/37	46/40	140	160	180	PUL	N	-	-	NIL	COMPLETED
18	18/F	5514	10.07.2013	24.09.2013	10WK	CAT-1	9.3	42/41	42/40	49/40	150	170	190	PUL	N	-	-	NIL	COMPLETED
24	36/M	5490	9.62013	30.06.2013	3WK	CAT-1	11	35/41	39/40	39/43	140	160	180	PUL	N	-	-	NIL	COMPLETED
25	58/M	5578	05.03.2013	10.05.2013	8WK 5DA	CAT-1	12	55/40	40/48	46/45	250	400	350	PUL	N	-	-	NIL	COMPLETED
26	45/F	5354	10.03.2013	12.04.2013	4WK 2DA	CAT-1	8	59/62	50/34	35/31	200	250	400	EXT.PUL	N	-	-	NIL	COMPLETED
27	40/M	5985	29.06.2013	13.07.2013	2WK	CAT-1	9	36/31	35/37	39/34	300	350	400	PUL	N	-	-	NIL	COMPLETED
28	45/M	5547	20.052013	04.06.2013	2WK	CAT-1	6.1	35/34	41/32	39/34	84	162	174	PUL	N	-	-	NIL	COMPLETED
29	32/F	5907	03.03.2013	05.05.2013	8WK 2DA	CAT-1	8.5	41/42	42/29	35/38	76	94	106	PUL	N	-	-	NIL	COMPLETED
30	34/M	11238	09.04.2013	14.05.2013	4WK 2DA	CAT-1	8.7	39/40	36/38	36/37	67	80	94	PUL	N	-	-	NIL	COMPLETED
31	24/F	11614	05.03.2013	09.04.2013	4WK 4DA	CAT-1	10.6	34/36	41/42	41/40	196	104	132	PUL	N	-	-	NIL	COMPLETED
32	25/F	6442	07.03.2013	10.05.2013	8WK 3DA	CAT-1	9	52/51	43/49	33/31	204	210	304	PUL	N	-	-	NIL	COMPLETED

33	30/F	4682	05.01.2013	06.03.2013	8WK 1DA	CAT-1	11.6	37/39	36/34	35/29	154	174	214	PUL	N	-	-	NIL	COMPLETED
34	52/M	3314	10.02.2013	30.03.2013	9WK	CAT-1	10.2	41/42	50/43	34/39	170	150	110	PUL	N	-	-	NIL	COMPLETED
35	42/M	6012	11.03.2013	31.03.2013	3WK	CAT-1	10.4	34/35	37/38	39/34	74	96	114	PUL	N	-	-	NIL	COMPLETED
36	42/F	6048	23.01.2013	31.03.2013	9WK 1DA	CAT-1	8	39/34	40/46	41/42	90	100	110	PUL	N	-	-	NIL	COMPLETED
37	41/M	6001	30.12.2012	02.02.2013	4WK	CAT-1	10	38/39	36/39	34/38	103	117	124	PUL	N	-	-	NIL	COMPLETED
38	28/M	6121	24.12.2012	07.01.2013	2WK	CAT-1	9.9	33/46	42/46	41/44	94	110	137	PUL	N	-	-	NIL	COMPLETED
39	55/F	6021	12.12.2012	21.02.2013	8WK 1DA	CAT-1	9.7	45/40	41/49	43/48	78	91	107	PUL	N	-	-	NIL	COMPLETED
40	53/M	6104	17.012013	29.03.2013	9WK	CAT-1	11	36/38	36/37	40/41	104	113	128	PUL	N	-	-	NIL	COMPLETED
41	32/F	3761	10.02.2013	15.04.2013	8WK 5DA	CAT-1	9.1	32/35	30/32	39/40	97	115	220	PUL	N	-	-	NIL	COMPLETED
42	35/M	2262	12.03.2013	04.04.2013	3WK 2DA	CAT-1	12	55/58	90/109	130/150	110	185	205	PUL	N	-	-	NIL	COMPLETED
43	40/M	4472	22.04.2013	25.05.2013	4WK 3DA	CAT-1	11.5	56/54	43/29	40/30	204	210	224	PUL	N	-	-	NIL	COMPLETED
44	34/F	3812	05.02.2013	15.04.2013	9WK 3DA	CAT-1	10.9	39/36	34/38	40/42	224	212	214	PUL	N	-	-	NIL	COMPLETED
45	37/M	5844	10.05.2013	14.07.2013	8WK 4DA	CAT-1	11.2	43/40	34/30	30/50	71	74	96	PUL	N	-	-	NIL	COMPLETED
46	23/M	5905	11.05.2013	12.07.2013	8WK 1 DA	CAT-1	10.8	30/39	38/50	40/47	90	114	90	EXT.PUL	-	-	-	NIL	COMPLETED
47	37/M	6078	16.05.2013	31.05,2013	2WK	CAT-1	13	40/41	39/40	44/42	251	262	264	PUL	N	-	-	NIL	COMPLETED
48	45/M	5797	10.03.2013	11.04.2013	4WKS	CAT-1	12	39/38	45/50	40/44	174	245	315	PUL	N	-	-	NIL	COMPLETED
49	25/F	5717	05.04.2013	07.06.2013	8WK 2DA	CAT-1	10.4	40/42	43/41	34/39	217	240	242	PUL	N	-	-	NIL	COMPLETED
50	55/F	5787	06.05.2013	08.07.2013	8WK 2DA	CAT-1	9	42/39	38/39	37/39	310	312	312	PUL	N	-	-	NIL	COMPLETED
51	48/F	5763	05.05.2013	04.07.2013	12WK	CAT-1	8.3	42/44	50/60	60/50	65	52	80	PUL	N	N	N	NIL	MDR-TB
52	34/F	5737	24.01.2013	28.03.2013	8WK 4DA	CAT-1	8.9	50/40	48/43	46/47	214	223	227	PUL	N	-	-	ANAEMIA	COMPLETED
53	38/F	6201	04.04.2013	06.05.2013	4WK2DA	CAT-1	9	48/36	112/234	99/78	204	226	258	EXT.PUL	-	-	-	HEPATITIS	COMPLETED
54	40/F	6475	17.06.2013	27.08.2013	5 WK 3DA	CAT-1	10.1	43/48	43/41	39/29	69	69	100	PUL	N	-	-	NIL	COMPLETED
55	35/F	3808	01.07.2013	04.09.2013	8WK 3DA	CAT-1	9.8	44/42	43/41	45/43	148	170	260	PUL	N	-	-	NIL	COMPLETED
56	30/F	6400	05.08.2013	20.05.2013	2WK1DA	CAT-1	10.3	45/43	37/40	43/49	180	273	312	PUL	N	-	-	NIL	COMPLETED
57	37/M	6462	23.08.2013	23.09.2013	4WK	CAT-1	11	43/39	39/33	36/36	120	174	201	PUL	N	-	-	NIL	COMPLETED
58	52/M	5254	20.11.2013	21.03.2013	8WK 1DA	CAT-1	12	41/38	40/47	41/42	114	121	139	PUL	N	-	-	NIL	COMPLETED
59	42/M	6828	04.09.2013	10.12.2013	10WK5DA	CAT-1	10	50/54	55/51	52/42	134	150	160	PUL	N	-	-	NIL	COMPLETED
60	47/M	6902	11.10.2013	6.1.2014	10WE5DA	CAT-1	11.1	48/45	43/39	41/38	116	132	141	PUL	N	-	-	NIL	COMPLETED

KEY WORDS FOR MASTER CHART

DUR – INTERVAL BETWEEN ATT AND ART

TB RX – TUBERCULOSIS TREATMENT

IRIS - IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

HB - HAEMOGLOBULIN

TC - TOTAL COUNT

ESR - ERYTHROCYTE SEDIMENTATION RATE

B.UREA – BLOOD UREA

S.CREAT –SERUM CREATININE

PUL – PULMONARY TUBERCULOSIS

EXT.PUL – EXTRA PULMONARY TUBERCULOSIS

INC.PLU.EFF –INCREASED PLEURAL EFFUSION

INC.PUL.INF- INCREASED PULMONARY INFILTRATES

ETHICAL COMMITTEE APPROVAL

K.A.P.VISWANATHAM GOVT. MEDICAL COLLEGE
TIRUCHIRAPALLI -1
INSTITUTIONAL ETHICS COMMITTEE

CERTIFICATE OF CLEARANCE

This is to certify that the project work titled **Early versus delayed initiation of ART for HIV infected individuals with tuberculosis on ATT** proposed by **Dr.Lawrence** part of fulfillment of M.D/M.S course in the subject of **Medicine** for the year **2012-2015** by The Tamilnadu Dr.MGR Medical University has been cleared by the ethics committee.

CHAIRMAN,
Institutional Ethics Committee
K.A.P.Viswanatham Govt. Medical College, Tiruchirapalli -1

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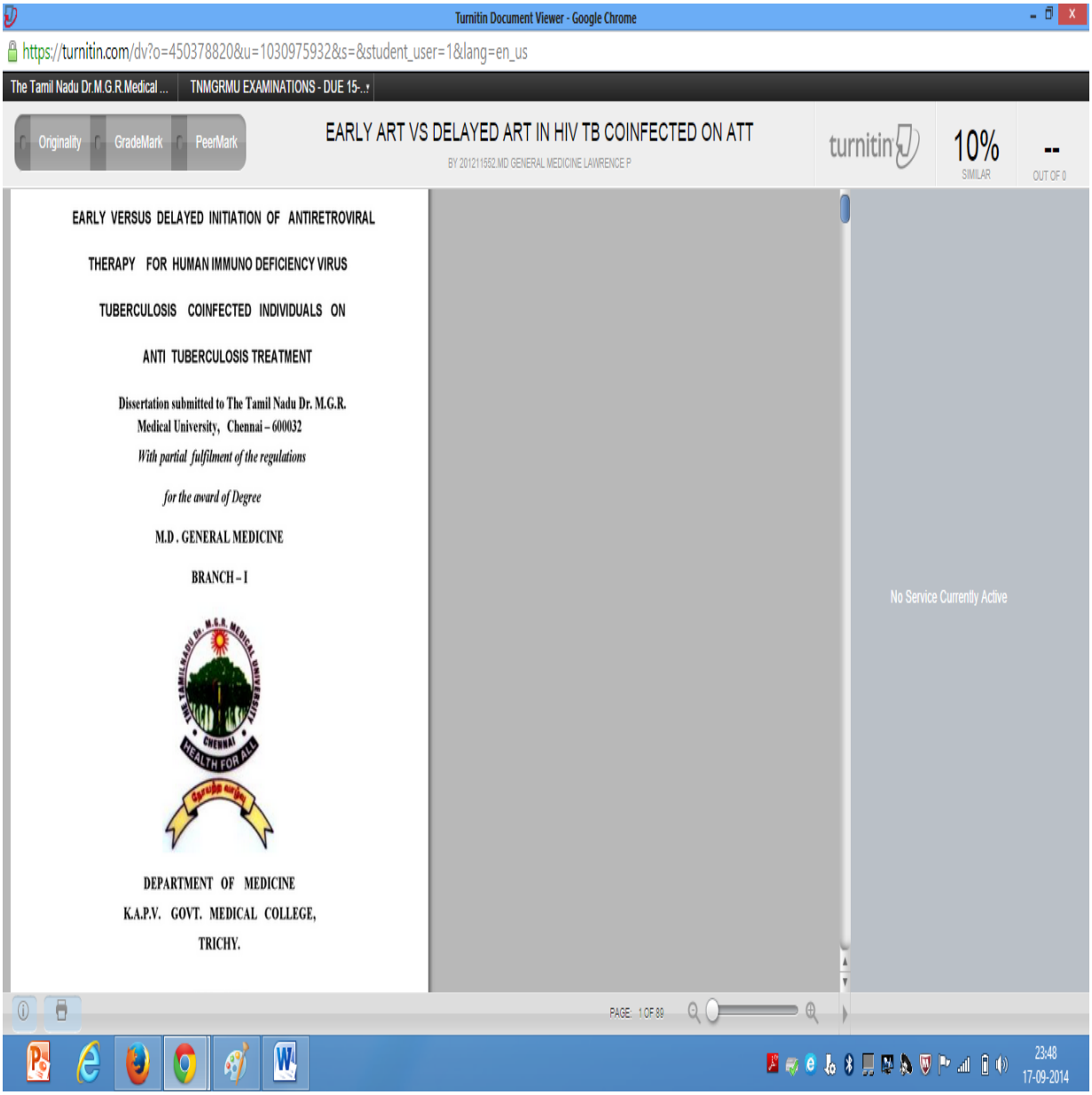
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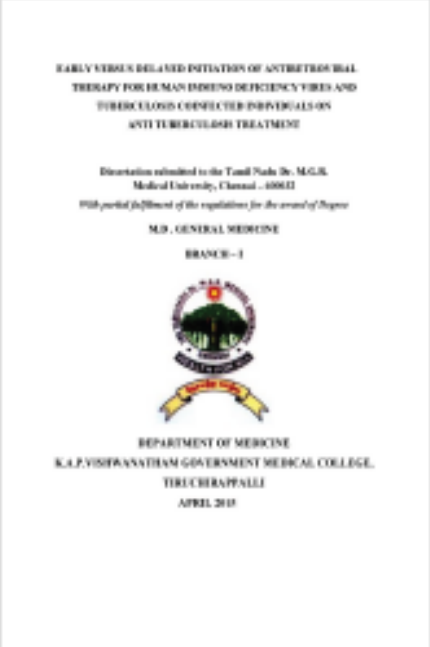
File name:	dr_lawrence_md_gen_med.docx
File size:	710.04K
Page count:	115
Word count:	14,228
Character count:	79,541
Submission date:	20-Sep-2014 12:33PM
Submission ID:	450378820



EARLY VERSUS DELAYED INITIATION OF ANTIRETROVIRAL THERAPY FOR HUMAN IMMUNO DEFICIENCY VIRUS AND TUBERCULOSIS CONFECTED INDIVIDUALS ON ANTI TUBERCULOSIS TREATMENT

Dissertation submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai - 600032

With partial fulfilment of the regulations for the award of Degree

M.D. GENERAL MEDICINE

BRANCH – I

DEPARTMENT OF MEDICINE
K.A.P.VISWANATHAM GOVERNMENT MEDICAL COLLEGE,
TIRUCHIRAPPALLI
APRIL 2013

ABBREVIATIONS

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3TC-LAMIVUDINE

AIDS- ACQUIRED IMMUNODEFICIENCY SYNDROME

AFB- ACID FAST BACILLI

ANC- ANTE NATAL CLINIC

ART- ANTIRETROVIRAL THERAPY

ARVS - ACUTE RETROVIRAL SYNDROME

ATT- ANTI TUBERCULOSIS TREATMENT

ATV/R- RITONAVIR-BOOSTED ATAZANAVIR

BCG- BACILLUS CALMETTE–GUÉRIN

cART- COMBINATION ANTI RETROVIRAL THERAPY

CD- CLUSTER OF DIFFERENTIATION

CDC- CENTRE FOR DISEASE CONTROL

CMI- CELL MEDIATED IMMUNITY

CNS – CENTRAL NERVOUS SYSTEM

d4T-STAVUDINE

DC- DENDRITIC CELL

DNA – DEOXYRIBO NUCLEIC ACID

DOTS – DIRECTLY OBSERVED THERAPY SHORT COURSE

EFV- EFAVIRENZ

EIA – ENZYME IMMUNOSORBENT ASSAY

EPTB- EXTRA PULMONARY TUBERCULOSIS

FDA- FOOD AND DRUG ADMINISTRATION

FTC- EMTRICITABINE

GIT – GASTEROINTESTINAL SYSTEM

HAART – HIGHLY ACTIVE ANTI RETROVIRAL THERAPY

HIV - HUMAN IMMUNODEFICIENCY VIRUS

ICMR – INDIAN COUNCIL OF MEDICAL RESEARCH

INC PLU- INCREASED PLEURAL EFFUSION

INC PUL- INCREASED PULMONARY INFILTRATES

IRIS- IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

LPV/R- LOPINAVIR/RITONAVIR

MDR TB- MULTIDRUG RESISTANT TUBERCULOSIS

MM – MONOCYTE MACROPHAGE

MTCT – MOTHER TO CHILD TRANSMISSION

NACO – NATIONAL AIDS CONTROL ORGANISATION

NNRTI – NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR

NRTI – NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR

OI- OPPURTUNISTIC INFECTION

PGLA- PERSISTENT GENERALISED LYMPH ADENOPATHY

PI- PROTEASE INHIBITOR

PLWHA- PEOPLE LIVING WITH HIV AND AIDS

PTB- PULMONARY TUBERCULOSIS

RNA – RIBONUCLEIC ACID

SAPIT – STARTING ANTIRETROVIRAL THERAPY AT THREE POINTS IN TUBERCULOSIS

SIMD-STAGE OF IMMUNODEFICIENCY

SIV – SIMIAN IMMUNODEFICIENCY VIRUS

STD- SEXUALLY TRANSMITTED DISEASE

TB –TUBERCULOSIS

TDF- TENOFOVIR

UNAIDS- THE JOINT UNITED NATIONS PROGRAMME ON HIV AND AIDS

VLPS-VIRUS LOW PRODUCTIVE SUBDUED

VNPL- VIRUS NON- PRODUCTIVE LATENT

WHO- WORLD HEALTH ORGANISATION

XDR TB- EXTENSIVELY DRUG RESISTANT TUBERCULOSIS